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EXPERIMENTS ON THE PROPERTIES OF THE EXTRINSIC FACTOR AND ON THE REACTION OF CASTLE

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The effectiveness of an incubated mixture of meat and normal human gastric juice against anemia was first described by Castle [1] in 1929.

In the original hypothesis it was assumed that a protein-like substance in the meat was split up by a proteolytic ferment of the normal gastric juice, either in vivo in the normal stomach or in vitro by incubation at 37 C., with formation of the effective antianemic substance. It was assumed by most authors that this newly formed substance was identical with the antianemic factor in liver, although this identity was not expressly stated by Castle.

The active factor in normal human gastric juice (called the intrinsic factor) was found to be thermolabile (it was destroyed by a temperature of 60 C. in one-half hour). This intrinsic factor was not identical with either of the known ferments pepsin and rennin.

The active factor in the meat (called the extrinsic factor) was thermostable.

In 1933, Klein and Wilkinson [2] claimed to have proved the formation of the antianemic factor in liver by incubation of meat and hog gastric mucosa in vitro. This claim was based on two types of experiments. In the first type the incubated mixture of meat and hog mucosa (containing the intrinsic factor) was heated to 60 or 65 C. for one-half hour without loss of activity.

These experiments have been criticized by Castle. He showed that heating of the incubated mixture at 80 C. for one-half hour invariably destroyed the activity. This temperature would not affect the antianemic liver factor if it had been formed in the incubated mixture.

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1. Castle, W. B.: Am. J. M. Sc. **178**:748, 1939.
2. Klein, L., and Wilkinson, J. F.: Biochem. J. **28**:1684, 1934.

Castle, Heath, Strauss and Heinle [3] attributed the positive results obtained by Klein and Wilkinson [2] to the too low degree of heating and to a possible slight protective activity of the proteins of the meat on the intrinsic factor.

In the second experiment of Klein and Wilkinson an attempt was made to isolate the newly formed antianemic liver factor from the incubated mixture; they added 70 per cent alcohol, filtered the mixture and concentrated the filtrate in vacuo. Finally, the concentrated filtrate was precipitated with 96 per cent alcohol. The precipitate was dissolved in water and injected into a patient with pernicious anemia, with a subsequent increase of reticulocytes, hemoglobin and erythrocytes. This result cannot be accepted as proof of the effectiveness of their product, because the reticulocytic peak occurred only on the nineteenth day of treatment, much too late to indicate a real effectiveness of the preparation injected.

In a recent article, Wilkinson, Klein and Ashford [4] described an experiment of the same type. Meat was incubated with human stomach tissue, and a product isolated in the manner described was given orally to a patient with pernicious anemia. A reticulocytic crisis on the eighth day and a rather slow increase of hemoglobin and erythrocytes resulted. Although this experiment has much more value than those previously described, it was not controlled by ingestion of the same amount of normal human stomach tissue without incubation with meat.

In 1936, Greenspon [5] criticized Castle's findings. He claimed that the antianemic principle is secreted by the stomach but that it is destroyed by peptic digestion and is protected against this destruction by addition of the proteins of the meat. This criticism has been refuted by Castle and others. It was shown that neutralized gastric juice alone is inactive if certain precautions are taken.

During these controversies some new interesting facts have been described, mainly by Castle, Heath, Strauss and Heinle.[3]

1. The mixture of meat and gastric juice was effective without incubation.

2. The mixture of meat and gastric juice was effective at a neutral reaction, whereas it was not effective if the reaction was strongly acid (p_H 1.8 to 2.5).[3]

3. When meat and gastric juice were given separately with an interval of no more than six hours a positive therapeutic effect was observed.

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3. Castle, W. B.; Heath, C. W.; Strauss, M. B., and Heinle, R. W.: Am. J. M. Sc. **194**:618, 1937.

4. Wilkinson, J. F.; Klein, L., and Ashford, C. A.: Quart. J. Med. **7**:555, 1938.

5. Greenspon, E. A.: Nature of Antipernicious Anemia Principle in Stomach: Method to Improve Stomach Preparations, J. A. M. A. **106**:266 (Jan. 25) 1936.

As a result of these findings, the original hypothesis of Castle had to be reconsidered. Castle stated recently that the site and mode of interaction between the extrinsic factor and the intrinsic factor are not yet known, although the site is probably in the gastrointestinal tract. Taylor, Castle, Heinle and Adams [6] demonstrated a close chemical resemblance between the intrinsic factor and a proteolytic ferment of the gastric juice acting at neutral reaction. Obviously the identity of the intrinsic factor with this proteolytic ferment is considered in this article, although it is not expressly stated. Acceptance of this identity would imply the formation of a new intermediary substance, which finally would be transformed into the antianemic liver factor.

PLAN OF INVESTIGATION

The experiments reported in this paper were started in 1936. They were based on the theory, prevailing at that time, of an in vitro formation of the antianemic liver factor in the gastric juice–meat mixture. It was thought probable that the chemical behavior of the extrinsic factor would be changed by transformation into the antianemic liver factor. A comparative study of the chemical properties of the extrinsic factor and the liver factor was planned.

Isolation and study of the liver factor have been advanced by many investigators, but a systematic investigation of the extrinsic factor has not been published. Castle demonstrated the solubility of the extrinsic factor from marmite (an autolyzed yeast extract) in 80 per cent alcohol. In the present observations this principle was applied to the extrinsic factor of meat. It was found possible to obtain extracts which were active after addition of normal gastric juice in the following manner.

Two hundred and fifty grams of beef was minced and mixed with a small quantity of water. To the resulting meat pulp concentrated alcohol was added until a concentration of 70 per cent was reached. The mixture was kept overnight and filtered next morning. The filtrate was distilled in vacuo. In the following observations, the resulting white turbid fluid will be called 70 per cent alcoholic extract of meat.

Normal human gastric juice which had been carefully neutralized immediately after removal from the stomach and had been kept in an ice box if necessary (for a maximum of three or four days) was used in all experiments.

Incubation for four hours was applied in experiments 1 and 2. In the subsequent experiments of the first series the incubation, which appeared to be unnecessary, was omitted.

In the first series of experiments the properties of the extrinsic factor in meat were studied. In the second series the nature of the reaction between the extrinsic factor and the intrinsic factor was investigated.

In all experiments which will be reported as test cases the patients had typical pernicious anemia in relapse, associated with achylia gastrica which was refractory to histamine (except the patient in experiment 3). A survey of the cases of these patients is given in table 1. Further clinical details will not be reported, as a typical response to therapy was obtained in all cases, either by administration of mixtures of the extrinsic and the intrinsic factor or by injection of liver preparations. In order to exclude ingestion of large amounts of the extrinsic factor, during the

6. Taylor, F. H. L.; Castle, W. B.; Heinle, R. W., and Adams, M. A.: J. Clin. Investigation **17**:335, 1938.

test periods no meat was included in the diet of the patients. All preparations were given in the morning to the fasting subject, and a light breakfast without tea was allowed one and one-half hours after the ingestion.

PROPERTIES OF EXTRINSIC FACTOR

EXPERIMENT 1 (patient P. G.).—In the first period, a mixture of washed human erythrocytes (30 cc.) with 150 cc. of gastric juice was administered daily for nineteen days by stomach tube, without therapeutic effect. The meaning of this negative result will be discussed in a forthcoming article. The therapeutic inactivity of gastric juice, alone or mixed with inactive proteins, is shown by this first period.

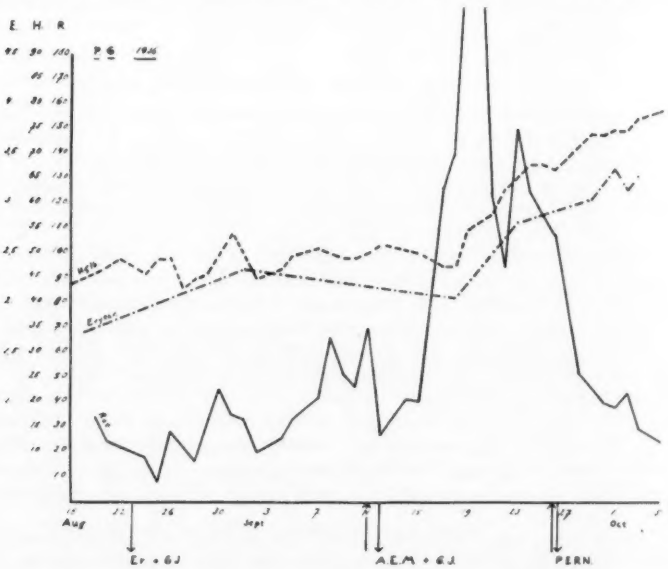

Chart 1 (experiment 1).—In the first period, 30 cc. of washed centrifuged human erythrocytes (Er.) and 130 cc. of gastric juice (G.J.) was given daily from Aug. 23 to Sept. 11, 1936. In the second period, 70 per cent alcoholic extract of meat (A.E.M.) and 150 cc. of gastric juice was given daily from September 12 to 26. Pernaemon was injected daily from September 26. (In this and in the following charts, gastric juice is indicated by the letters G.J., alcoholic extract of meat by the letters A.E.M., and injection of the liver preparation pernaemon by the letters PERN.)

In the second period, a mixture of 70 per cent alcoholic extract of meat (250 Gm.) and 150 cc. of gastric juice, incubated for four hours at 37 C., was administered daily to the fasting subject. A typical reticulocyte crisis with an increase of hemoglobin and erythrocytes followed (chart 1). When the reticulocyte crisis had disappeared, injections of a liver concentrate (pernaemon) were given daily, without further effect on the reticulocytes. A maximum therapeutic response was obtained in this manner.

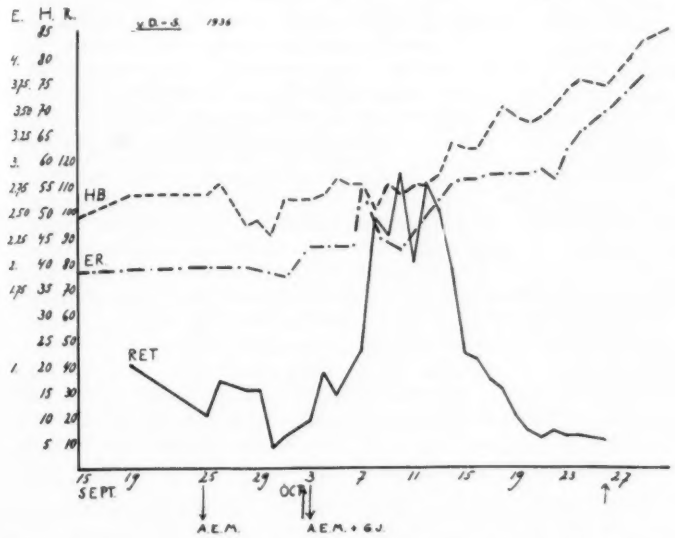

Chart 2 (experiment 2).—In the first period, 70 per cent alcoholic extract of meat (250 Gm.) was given daily from Sept. 24 to Oct 2, 1936. In the second period, 70 per cent alcoholic extract of meat (250 Gm.) and 50 cc. of gastric juice was given daily from October 3 to 26.

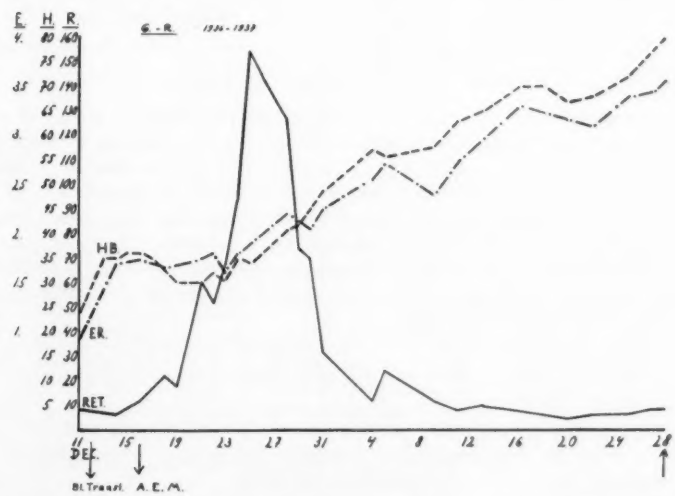

Chart 3 (experiment 3).—A blood transfusion was given on Dec. 12, 1936. Seventy per cent alcoholic extract of meat (250 Gm.) was given daily from Dec. 16 to Jan. 28, 1937.

EXPERIMENT 2 (patient v. D. S.).—In the first period, 70 per cent alcoholic extract of meat (250 Gm.), without gastric juice, was given. There was no therapeutic effect. In the second period, 70 per cent alcoholic extract of meat (250 Gm.) mixed with 50 cc. of gastric juice incubated for four hours at 37 C. was administered daily. Again a marked therapeutic result was seen; the typical reticulocyte crisis was followed by a marked increase of hemoglobin and erythrocytes (chart 2).

EXPERIMENT 3 (patient G. R.).—In this patient severe anemia developed during pregnancy. She came into the ward in a severely anemic condition immediately after delivery. The blood picture was typical of pernicious anemia. Megaloblasts were present. The color index was elevated. However, free hydrochloric acid was found in the stomach. The diet had been insufficient during pregnancy; the patient had eaten scarcely any meat. The condition was considered to be a typical pernicious anemia of pregnancy, caused by relatively insufficient ingestion of the extrinsic factor. A blood transfusion was given, followed by administration of a mixture of alcoholic extract of meat (250 Gm.) without gastric juice. In contrast with the results in experiment 2, a typical therapeutic response was seen, which was attributed to ingestion of the extrinsic factor alone by this patient with normal gastric juice. It was considered improbable that this response had anything to do with the preceding blood transfusion (chart 3).

Comment on Experiments 1, 2 and 3.—The presence of the extrinsic factor in the 70 per cent alcoholic extract of meat is proved by these experiments. The therapeutic response of the mixture with only 50 cc. of gastric juice in experiment 2 facilitated the subsequent experiments. In most cases 75 cc. of gastric juice was used.

In the following experiments an attempt was made to precipitate the extrinsic factor with 96 per cent alcohol, without success. Not all experiments with negative results are reported. The only questionable response was observed in the following experiment.

EXPERIMENT 4 (patient P. F.).—Seventy per cent alcoholic extract of meat (500 Gm.) was treated with absolute alcohol until a concentration of 96 per cent was reached and then was filtered. The precipitate (*a*) was disolved in water; the filtrate (*b*) was distilled in vacuo. In the first period, the precipitate, *a* (of 500 Gm. of meat), was mixed with 100 cc. of gastric juice and administered daily to the patient for ten days. On the eleventh day a moderate reticulocyte response, without increase of hemoglobin or erythrocytes, followed. It is uncertain whether this late reticulocyte crisis was caused by the presence of a small amount of extrinsic factor in the precipitate.

In the second period, from the eleventh to the twentieth day, the filtrate, *b* (of 500 Gm. of meat), mixed with 100 cc. of gastric juice, was administered daily without any further effect.

In the third period, the 70 per cent alcoholic extract of meat (250 Gm.) with 75 cc. of gastric juice was administered daily for four days. The condition of the patient did not allow continuation of the experiment.

On injection of a liver concentrate a typical therapeutic response was obtained.

EXPERIMENT 5 (patient R. V.).—The 70 per cent alcoholic extract of meat (250 Gm.) was treated with 96 per cent alcohol as described for experiment 4. The precipitate (*a*) and the filtrate (*b*) were reunited and mixed with 75 cc. of gastric juice. This mixture was administered daily to the patient, without any result. On injection of pernaemon a typical therapeutic response was seen (chart 5).

Comment on Experiments 4 and 5.—Destruction of the extrinsic factor by 96 per cent alcohol is clearly shown by experiment 5. The possibility that this destruction is not complete must be accepted on the

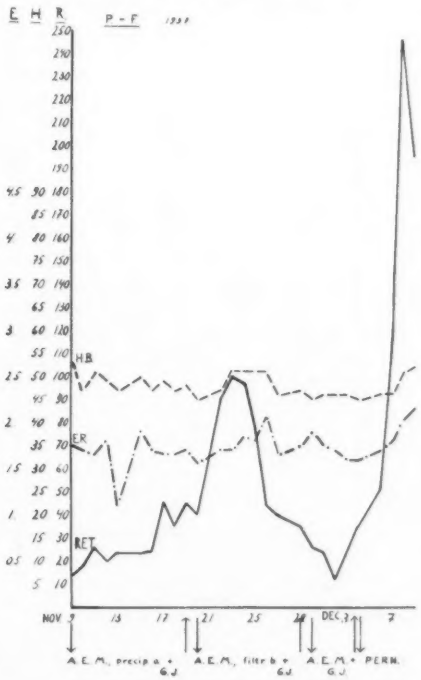

Chart 4 (experiment 4).—Seventy per cent alcoholic extract of meat (500 Gm.) was treated with 96 per cent alcohol (precipitate *a* and filtrate *b*). In the first period, precipitate (*a*) and 100 cc. of gastric juice was given daily from Nov. 9 to 19, 1937. In the second period, filtrate (*b*) and 100 cc. of gastric juice was given daily from November 20 to 29. In the third period, 70 per cent alcoholic extract of meat (250 Gm.) and 75 cc. of gastric juice was given daily from November 30 to December 4. Pernaemon was injected daily from December 4.

dubious evidence of experiment 4, with doubled quantities of the precipitate. For the study and isolation of the extrinsic factor this precipitation was deemed to be unfruitful. The sensitivity of the extrinsic factor to 96 per cent alcohol was quite unexpected.

The white turbidity of the alcoholic extract (after distillation in vacuo) suggested the presence of fats and lipoids, which inhibited to a certain extent the study of the extract. In the next experiment an attempt was made to remove the fats by ether extraction. In the same experiment the concentration of alcohol used in the first extraction was raised to 80 per cent.

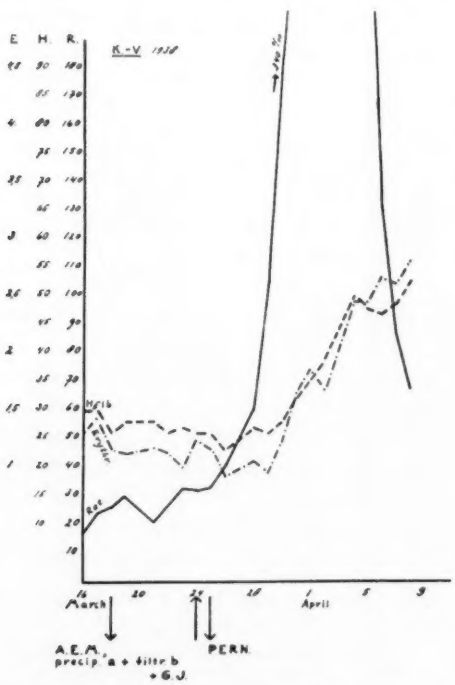

Chart 5 (experiment 5).—Seventy per cent alcoholic extract of meat (250 Gm.) was treated with alcohol, 96 per cent: the precipitate (*a*) and the filtrate (*b*) were reunited (see text); *a* + *b* and 75 cc. of gastric juice was given daily from March 18 to 24, 1938. Pernaemon was injected daily from March 25.

EXPERIMENT 6 (patient L. P.).—The 80 per cent alcoholic extract of meat (250 Gm.) was extracted with ether. The ether was separated from the fluid. The remaining fluid was centrifuged to remove a white precipitate at the bottom. The resulting slightly turbid fluid was mixed with 75 cc. of gastric juice and administered daily to the patient. An intense reticulocyte crisis (maximum, 28 per cent) and a fast rise in the concentration of hemoglobin and erythrocytes indicated a maximal response.

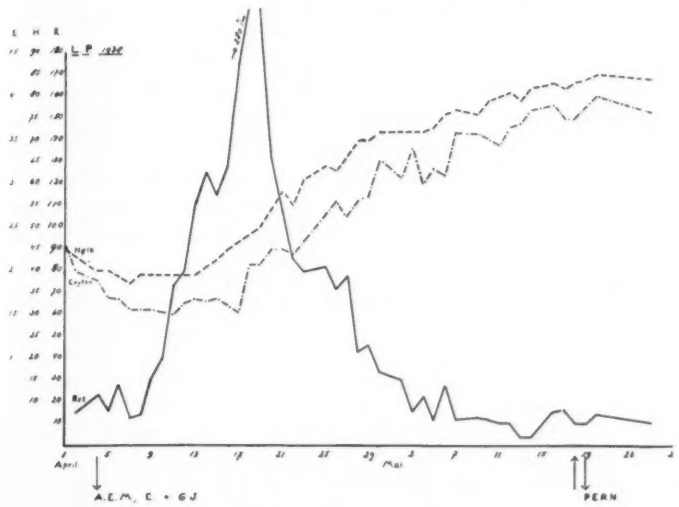

Chart 6 (experiment 6).—Eighty per cent alcoholic extract of meat (250 Gm.) extracted with ether (indicated by the letters A.E.M., E) and 75 cc. of gastric juice was given daily from April 4 to May 18, 1938. Pernaemon was injected daily from May 19.

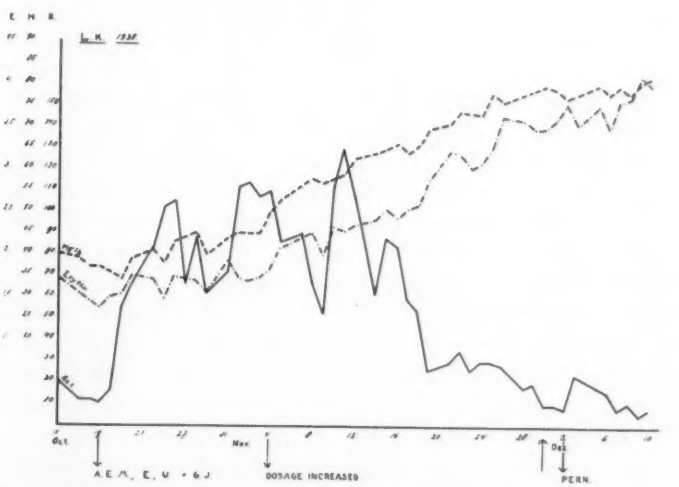

Chart 7 (experiment 7).—Eighty per cent alcoholic extract of meat (330 Gm.) extracted with ether and ultrafiltered (indicated by the letters A.E.M., E., U.) and 75 cc. of gastric juice was given daily from Oct. 19 to Nov. 4, 1938. The same preparation, originating from 500 Gm. of meat and 75 cc. of gastric juice was given daily from November 4 to 30. Pernaemon was injected daily from December 2.

Comment.—The ether-soluble substances can be removed from the alcoholic extract without loss of activity. The activity of an 80 per cent alcoholic extract of meat was proved in the same experiment.

The results of ultrafiltration on extracts containing the extrinsic factor have not been reported in the literature. The following experiment is of importance in deciding finally whether the extrinsic factor may be a protein-like substance, as was originally assumed by Castle. This experiment was made possible by the preceding ether extraction.

EXPERIMENT 7 (patient L. K.).—The 80 per cent alcoholic extract of meat (330 Gm.) was extracted with ether. The remaining watery fluid was ultrafiltered in collodion sacs. The ultrafiltrate was mixed with 75 cc. of gastric juice and administered to the patient daily. A clearcut but irregular reticulocyte crisis followed, but there was only a slow rise of the concentration of hemoglobin and erythrocytes. Consequently, on the twentieth day the daily dose of ultrafiltrate was raised to a dose obtained from 500 Gm. of meat mixed with the same amount (75 cc.) of gastric juice. A new reticulocyte crisis followed, together with a fast increase of hemoglobin and erythrocytes.

Comment.—The experiment clearly shows that the extrinsic factor passes through an ultrafilter. During this procedure a loss of activity is apparent. In a second experiment, not reported in detail, exactly the same results were obtained—a positive effect of the ultrafiltrate, but only in a higher dose than that of the original extract.

The cause of this loss of activity during ultrafiltration was not clear at first. The majority of the substances present in the original alcoholic extract passed through the ultrafilter, as will be seen from table 1. Only a small fraction of the fluid remained in the filter. The possibility of partial absorption of the extrinsic factor by the collodion sac was considered. In another experiment, which will be reported later (experiment 15, third period), physiologic solution of sodium chloride was added to the remainder of the fluid in the collodion sacs, and the ultrafiltration was then continued. The ultrafiltrate obtained was mixed with the first ultrafiltrate and with 75 cc. of gastric juice and administered to the patient. The combined ultrafiltrates of 330 Gm. of meat were given in this manner. A marked therapeutic response was seen. This experiment suggests the possibility that the amount of the effective substance present in the ultrafiltrate is increased by washing.

The next step in analysis of the extrinsic factor was precipitation of the alcoholic meat extract with saturated ammonium sulfate. Less than one tenth of the substance originally present in the extract was precipitated in this manner.

TABLE 1.—*Data on Patients with Pernicious Anemia Used as Test Subjects*

Experiment No.	Initials of Patient	Sex	Age	Free HCl in Stomach (with Histamine Injection)	Initial Blood Picture							Complications
					Hemoglobin, %	Red Blood Cells, Millions per Cu. Mm.	Reticulocytes, %	Anisocytosis	Poikilocytosis	Normoblasts	Megaloblasts	
1	P. G.	M	43	—	44	1.70	3.4	++	++	—	—	
2	v. D. S.	F	54	—	49	1.92	4.0	++	++	—	1	
3	G. R.	F	28	+	24	0.96	0.8	+++	+++	4	3	Pernicious anemia of pregnancy
4	P. S.	F	57	—	55	1.94	0.4	+	+	1	—	
5	K. V.	F	55	—	33	1.32	1.8	++	++	2	1	
6	L. P.	M	55	—	33	1.33	2.0	+	+	5	3	Tropical sprue
7	L. K.	M	58	—	43	1.56	2.0	+	+	1	—	Auricular fibrillation
8	S. M.	M	57	—	50	1.79	0.4	+++	+	—	—	
9	J. P.	M	60	—	68	2.92	0.8	+	+	1	—	
10	J. S.	M	61	—	67	1.72	3.8	+	+	1	1	
11	B. K.	F	62	*	34	1.71	0.6	++	zw.+	—	—	Polyneuritis
12	K. S.	F	60	—	26	1.30	1.2	++	++	4	3	
13	J. B.	M	81	—	44	1.44	0.6	+	+	—	—	
14	v. B. M.	F	37	—	31	1.23	1.6	+++	+++	4	8	
15	J. R.	M	46	—	44	1.17	5.0	+	+	9	—	

* Investigation of the stomach was refused by the patient. In 1933 there was no free hydrochloric acid; no histamine was given.

EXPERIMENT 8 (patient S. M.).—The 80 per cent alcoholic extract of meat (330 Gm.) was extracted with ether and afterward saturated with ammonium sulfate. The precipitate was separated by decantation and centrifugation and finally dissolved in water. This solution was mixed with 75 cc. of gastric juice and administered daily to the patient.

A moderate reticulocytic rise was observed, with a maximum on the tenth day, but only a slight increase of the hemoglobin values occurred, without any change in the number of erythrocytes. On the fifteenth day the amount of precipitate was increased one and one-half times (e. g., the precipitate originating from 500 Gm. of meat was given daily). A second reticulocyte crisis was seen, together with a steady increase of hemoglobin and erythrocytes. About one month afterward an injection of pernaemon was given, without any effect on the reticulocytes.

EXPERIMENT 9 (patient L. P.).—In this experiment a high initial value for hemoglobin was present; therefore, marked results could not be expected.

In the first period, gastric juice was treated with 70 per cent alcohol, and the resulting fractions were reunited; 80 per cent alcoholic extract of meat (250 Gm.) was added. The mixture was administered to the patient. The reader is referred to experiment 15 (first period) for a more detailed description and for a discussion of its meaning. The result was considered to be negative. The slight increase in number of reticulocytes, which was almost maximal on the fourth day, could not be attributed to this preparation, for it was too early. At the same time a fall in the number of erythrocytes occurred.

In the second period, beginning on the eleventh day, the ammonium sulfate precipitate from the 80 per cent alcoholic extract of meat (500 Gm.), as described for experiment 8, was mixed with 75 cc. of gastric juice and administered daily to the patient. A moderate reticulocyte crisis with a marked increase of hemoglobin and erythrocytes followed.

EXPERIMENT 10 (patient J. S.).—In the first period, a fraction of the ammonium sulfate precipitate (the nonultrafiltrable rest) was given, together with 75 cc. of gastric juice. This fraction seemed to be inactive; although a slight increase of reticulocytes was present on the eighth day, a slight but steady decrease of hemoglobin and erythrocytes occurred.

In the second period, beginning on the fourteenth day, the ammonium sulfate precipitate from the 80 per cent alcoholic extract of meat (500 Gm.), as described for experiment 8, was mixed with 75 cc. of gastric juice and administered daily to the patient. A marked reticulocyte crisis with a maximum on the eleventh day followed, but there was no corresponding increase of hemoglobin and erythrocytes. On the thirty-fourth day an injection of the liver extract pernaemon was given; a second sharp reticulocyte crisis with increase of erythrocytes and hemoglobin followed.

Comment on Experiments 8, 9 and 10.—In these experiments the result of the ammonium sulfate precipitate of the 80 per cent alcoholic meat extract was studied. In experiment 8 it was found that the precipitate from 330 Gm. of meat daily was insufficient for a good therapeutic result. The precipitate from 500 Gm. of meat daily gave a good result in this patient.

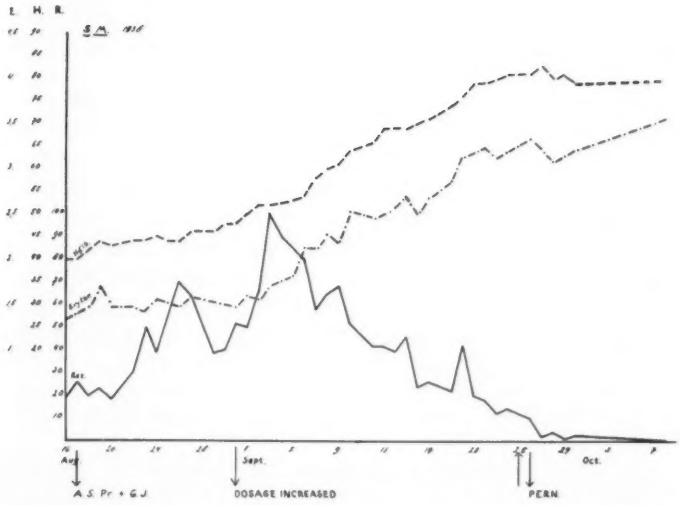

Chart 8 (experiment 8).—Eighty per cent alcoholic extract of meat (330 Gm.) extracted with ether, precipitated by saturation with ammonium sulfate (indicated by the letters A.S.Pr.) and 75 cc. of gastric juice was given daily from Aug. 17 to 31, 1938. The same preparation, originating from 500 Gm. of meat and 75 cc. of gastric juice, was given daily from August 31 to September 25. Pernaemon was injected daily from September 26.

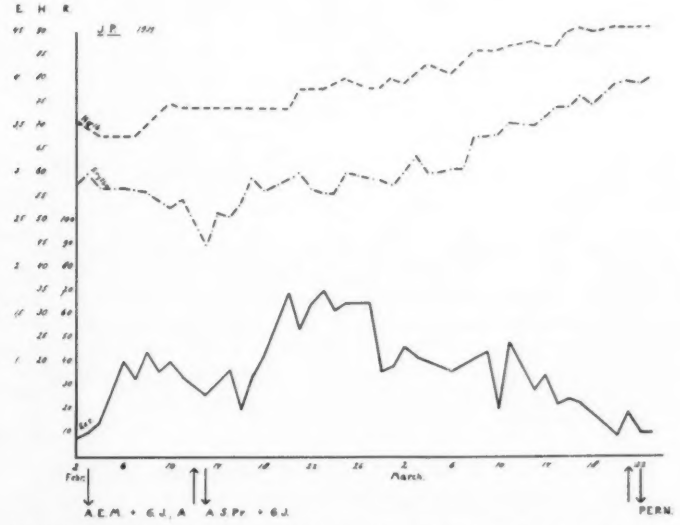

Chart 9 (experiment 9).—In the first period, 80 per cent alcoholic extract of meat (250 Gm.) and 75 cc. of gastric juice (treated with 70 per cent alcohol, indicated by the letters G.J., A.) was given daily from Feb. 3 to 12, 1939. In the second period, ammonium sulfate precipitate (A.S.Pr.) from 500 Gm. of meat (same preparation as in experiment 8) and 75 cc. of gastric juice was given daily from February 13 to March 21. Pernaemon was injected daily from March 22.

In experiment 9 the ammonium sulfate precipitate from 500 Gm. of meat was administered daily, with a satisfactory therapeutic result.

In experiment 10 the same amount of ammonium sulfate precipitate gave a marked reticulocytic crisis, but without a rise in concentration of hemoglobin and erythrocytes.

These experiments show that the extrinsic factor is present in the ammonium sulfate precipitate but that loss of more than 50 per cent of the active substance occurs. It was considered probable that in experiment 10 a further increase in the amount of precipitate daily

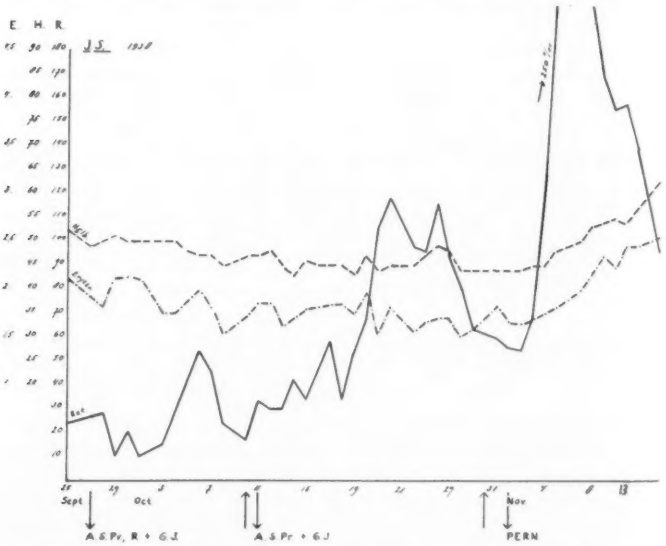

Chart 10 (experiment 10).—The ammonium sulfate precipitate originating from 500 Gm. of meat (same preparation as in experiment 8) was ultrafiltered and separated into an ultrafiltrate and a nonultrafiltrable rest (A.S.Pr., R.). In the first period, the latter preparation (A.S.Pr., R.) and 75 cc. of gastric juice was given daily from Sept. 27 to Oct. 10, 1938. In the second period, the ammonium sulfate precipitate originating from 500 Gm. of meat (A.S.Pr.) and 75 cc. of gastric juice was given daily from October 10 to 30. Pernaemon was injected daily from November 1.

administered would have given a good therapeutic effect, but this experiment could not be extended any longer.

An investigation of the fractions obtained by ultrafiltration and by precipitation with ammonium sulfate showed that the nonultrafiltrable rest contained the major part of the substances which were precipitated

by ammonium sulfate. This fact is demonstrated in table 2. In this table the amount of substance present in the various fractions of a single extract is shown as an example.

Similar values were obtained with other extracts. The figures in table 2 show that 80 per cent of the small precipitate obtained with ammonium sulfate did not pass an ultrafilter; the extrinsic factor should be present in the very small fraction of the precipitate which passed the ultrafilter. Daily administration of this fraction (e. g., the ultrafiltrate of the ammonium sulfate precipitate obtained from 500 Gm. of meat) mixed with 75 cc. of gastric juice to a patient with pernicious anemia did not have any effect (experiment not reported in detail). The nonultrafiltrable rest of the ammonium sulfate precipitate was mixed

TABLE 2.—*Weight of Fractions Obtained in the Foregoing Experiments*

1 Kg. of Meat	Dry Substance, Gm./Kg.	Therapeutic Response
80% alcoholic extract	26.34	+
80% alcoholic extract after extraction with ether	19.44	+
Ether-soluble substances	7.00	..
80% alcoholic extract extracted with ether and ultrafiltrated; ultrafiltrate	17.04	+
80% alcoholic extract extracted with ether and ultrafiltrated; nonultrafiltrable rest	1.70	..
80% alcoholic extract extracted with ether and ultrafiltrated; nonultrafiltrable rest saturated with ammonium sulfate; precipitate	0.72	..
80% alcoholic extract extracted with ether and saturated with ammonium sulfate; precipitate	1.09	+
Ammonium sulfate precipitate of 80% alcoholic extract extracted with ether and ultrafiltrated; ultrafiltrate	0.13	—
Ammonium sulfate precipitate of 80% alcoholic extract extracted with ether and ultrafiltrated; nonultrafiltrable rest	0.91	—

with 75 cc. of gastric juice and administered during the first period of experiment 10, without clearcut effect. The lack of activity of these fractions is probably caused by the progressive loss of active substance in each fractionation, especially in the precipitation with ammonium sulfate. It is possible that the active substance is not truly precipitated by ammonium sulfate but is only partially absorbed by the other precipitated substances.

In the foregoing experiments an analysis of the extrinsic factor was attempted. In the following series of experiments Castle's reaction was analyzed.

ANALYSIS OF CASTLE'S REACTION

An attempt was made to isolate the antianemic substance from the incubated mixture of meat and gastric juice, as has been done by Wilkinson and Klein.

EXPERIMENT 11 (patient B. K.).—To the incubated mixture of alcoholic extract of meat (1 Kg.) and 400 cc. of gastric juice, concentrated alcohol was added until a con-

centration of 70 per cent was reached. The fluid was filtered and the filtrate concentrated in vacuo to a small volume. To the concentrate absolute alcohol was added until a concentration of 96 per cent was reached. The precipitate was collected, was dissolved in isotonic salt solution and, after careful sterilization by pasteurization at 70 C., was administered to the patient by intramuscular injection. The whole amount was given in four days. The result was wholly negative. There was no response of reticulocytes, hemoglobin or erythrocytes.

Comment.—The antianemic liver factor is soluble in 70 per cent alcohol and is precipitated by 96 per cent alcohol. These properties

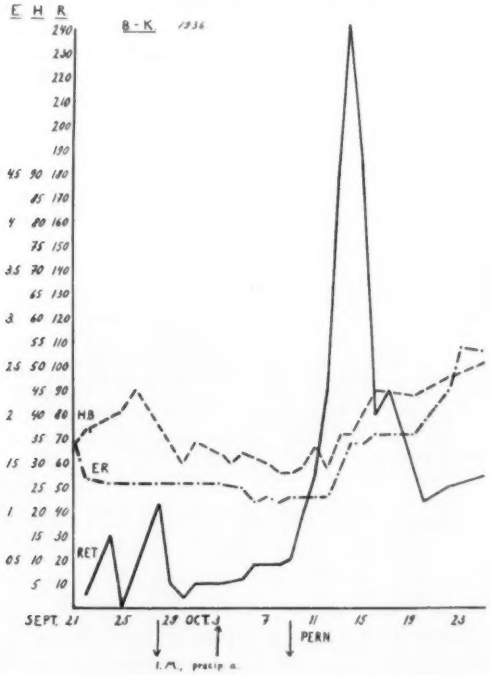

Chart 11 (experiment 11).—Precipitation of the incubated mixture of alcoholic extract of meat (1 Kg.) and gastric juice (400 cc.) with concentrated alcohol. The preparation, indicated by the letters I.M., precip. *a*, was given divided in several doses by intramuscular injection from Oct. 28 to Nov. 3, 1936. Pernaemon was injected daily from November 9.

were used to analyze the incubated mixture of meat and gastric juice for newly formed antianemic liver factor. The injection of the fraction thus isolated gave negative results, contrasting with the positive results obtained with a similar product by Wilkinson and Klein. The

possibility of loss of activity of the product during preparation for injection was considered.

EXPERIMENT 12 (patient K. S.).—The incubated mixture of meat (250 Gm.) and gastric juice was treated with 70 per cent alcohol and afterward with 96 per cent alcohol as described for experiment 11. The resulting precipitate was dissolved in isotonic salt solution and administered daily to the patient by mouth. Again the effect was absolutely negative.

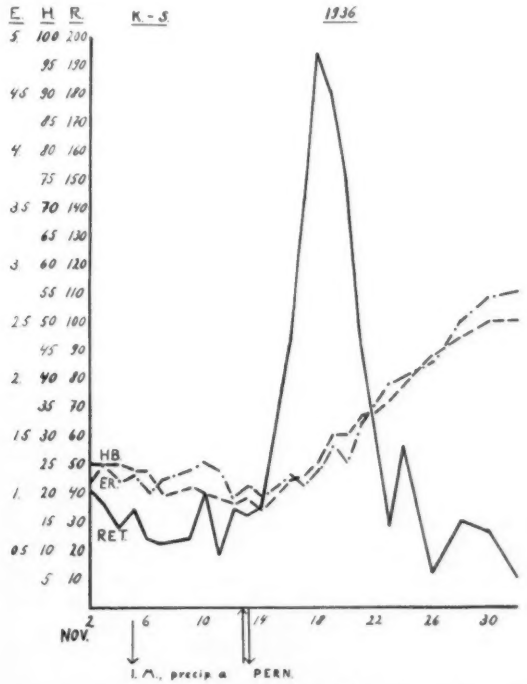

Chart 12 (experiment 12).—The same preparation as in experiment 11 (from 250 Gm. of meat), indicated by the letters I.M., precip. *a*, was given daily by mouth from Nov. 5 to 13, 1936. Pernaemon was injected daily from November 13.

Comment.—This experiment, together with experiment 11, demonstrates that in the 96 per cent alcoholic precipitate obtained from the incubated mixture no therapeutically active amount of liver factor is present.

In the next experiment the number of manipulations was still more restricted by omission of precipitation with 96 per cent alcohol.

EXPERIMENT 13 (patient J. B.).—To the incubated mixture of meat (250 Gm.) and gastric juice concentrated alcohol was added until a concentration of 70 per

cent was reached. The fluid was filtered, and the filtrate was concentrated in vacuo. The concentrate was administered daily to the patient. Again a therapeutic effect was absent.

Comment.—The absence of therapeutically active amounts of liver factor in the incubated mixture is still more clearly shown in this experiment. The possibility that an active substance with other properties had been formed was investigated in the next experiment.

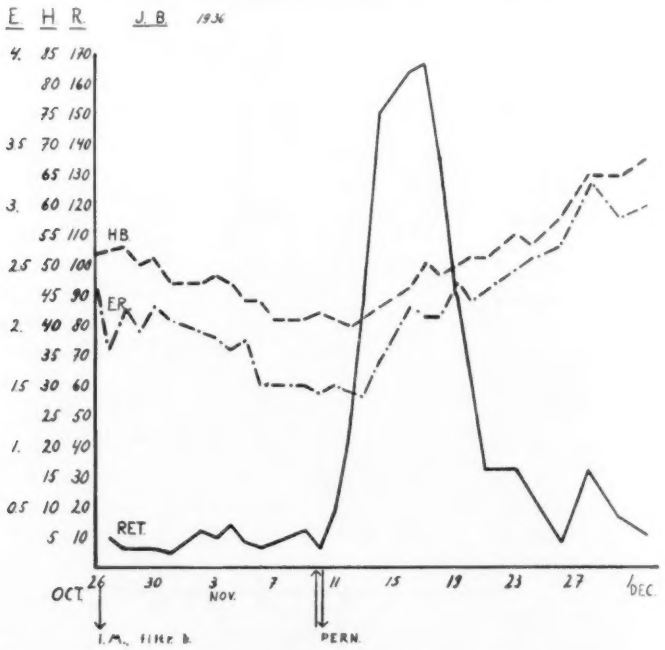

Chart 13 (experiment 13).—The incubated mixture of alcoholic extract of meat (250 Gm.) and gastric juice was treated with 70 per cent alcohol. The filtrate (indicated by the letters I.M., filtr. *b*) was given daily to the patient by mouth from Oct. 10 to Nov. 10, 1936. Pernaemon was injected daily from November 10.

Experiment 14 (patient v. B. M.).—To the incubated mixture of meat (250 Gm.) and gastric juice concentrated alcohol was added until a concentration of 70 per cent was reached. By filtration a filtrate (*a*) and a precipitate (*b*) were collected. The filtrate, *a*, was concentrated in vacuo. The precipitate, *b*, was dissolved in isotonic salt solution. Then the filtrate, *a*, and the precipitate, *b*, were reunited, and the mixture, containing all the original substance, was administered to the patient. Again a negative effect was observed.

Comment.—This experiment proves that the incubated mixture of meat and gastric juice, which is therapeutically active, is inactivated by treatment with 70 per cent alcohol and reunion of the two fractions. Inactivation of the incubated mixture by heating to 80 C. for one-half hour has already been described by Castle. The in vitro formation of the antianemic liver principle cannot be accepted any longer. Taylor, Castle, Heinle and Adams [6] demonstrated the proteolytic activity of

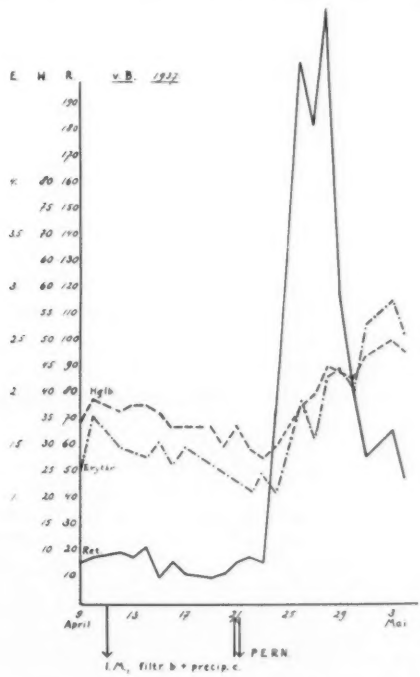

Chart 14 (experiment 14).—The incubated mixture of alcoholic extract of meat (250 Gm.) and gastric juice was treated with 70 per cent alcohol. The reunited filtrate and precipitate (indicated by the letters I.M., filtr. *b* + precip. *c*) was given daily to the patient by mouth from April 11 to 21, 1937. Pernaemon was injected daily from April 21.

neutralized gastric juice and the identical behavior of this ferment and the intrinsic factor in many respects. No conclusions are drawn from these experiments by the authors. However, it is evident that the actual identity of the newly found proteolytic ferment and the intrinsic factor is considered. The acceptance of this identity necessarily leads to the

conception of the formation of an intermediate factor (subsequently called X factor for convenience). This hypothesis can be expressed in the following manner:

Extrinsic factor	+	intrinsic factor	→	X-factor	→	liver factor
↓		↓		↓		↓
Thermostable		Thermolabile		Thermolabile		Thermostable
↓		↓		↓		↓
Soluble in 70 per cent alcohol		Inactivated by 70 per cent alcohol		Inactivated by 70 per cent alcohol		Soluble in 70 per cent alcohol

This sequence of events, although perhaps not impossible, is very improbable. It will be seen that the two properties known of the X factor, e. g., inactivation by heating to 80 C. and inactivation by treatment with 70 per cent alcohol, are also inherent to one of the constituents of the incubated mixture, e. g., the intrinsic factor (for proof of the inactivation of intrinsic factor by 70 per cent alcohol, compare the following experiment [15], first period). These experiments suggest strongly the possibility that in the incubated mixture no X factor is formed in vitro. If this is true, only an in vivo interaction between the extrinsic and the intrinsic factor can be assumed.

The absence of an intermediate X factor formed by the fermentive splitting of the extrinsic factor was further demonstrated in the next experiment (second period).

EXPERIMENT 15 (patient J. R.).—In the first period, demonstration of the inactivation of the intrinsic factor in the gastric juice by 70 per cent alcohol was done. To 75 cc. of gastric juice concentrated alcohol was added until a concentration of 70 per cent was reached. The mixture was filtered and the filtrate and precipitate were reunited in the manner previously described (experiment 14). The resulting fluid, containing all the substances originally present in the gastric juice, was mixed with alcoholic extract of meat (250 Gm.) and administered to the patient. This patient had a constant high level of reticulocytes in his blood, but administration of the mixture had no effect on the reticulocytes, hemoglobin or erythrocytes.

In the second period, the mixture of alcoholic extract of meat (500 Gm.) and 150 cc. of gastric juice was incubated for four hours. Afterward, ultrafiltration of the incubated mixture through collodion membranes was carried out. The nonfiltrable rest (about one-third of the original volume) was diluted with water and again ultrafiltered. In this manner no more than one-ninth of the ultrafiltrable substances could remain in the nonultrafiltrable portion of the fluid.

The ultrafiltrates were administered daily to the patient. The result was negative.

In the third period, the alcoholic extract of meat (330 Gm.) was first ultrafiltered. The small rest in the collodion sacs was diluted with physiologic solution of sodium chloride and again ultrafiltered. The first and second ultrafiltrates were mixed, and 75 cc. of gastric juice was added. The mixture was administered daily to the patient. A marked reticulocyte crisis occurred, together with a fast increase of hemoglobin and erythrocytes.

Comment on Experiment 15.—The first period shows clearly that treatment of the gastric juice with 70 per cent alcohol leads to inactivation of the intrinsic factor. This had already been shown in the first period of experiment 9, but this experiment was not so clearcut, owing to the nonspecific rise of the reticulocytes in the beginning of the experiment. It is possible that inactivation of gastric juice by 70 per cent alcohol is not complete.

In the second period the possible formation of an intermediate X substance by the enzymatic splitting of the extrinsic factor was investigated. The fact that the extrinsic factor passes through an ultrafilter was demonstrated in experiment 7 and was shown again in the third

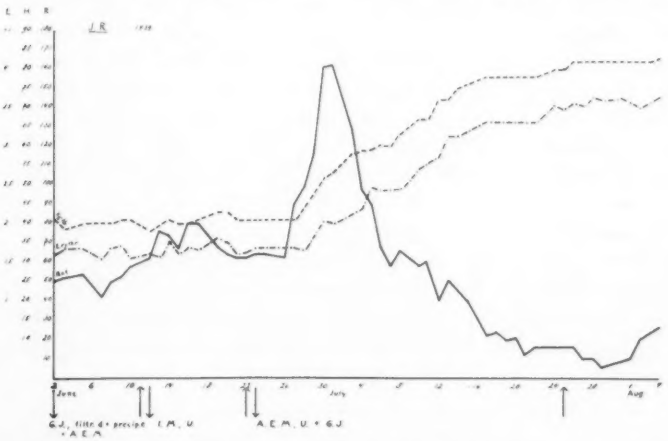

Chart 15 (experiment 15).—In the first period, gastric juice (75 cc.) was treated with 70 per cent alcohol. The reunited filtrate (*d*) and precipitate (*e*) were mixed with alcoholic extract of meat (250 Gm.) and given daily to the patient by mouth from June 2 to 11, 1939. In the second period, the incubated mixture of alcoholic extract of meat (500 Gm.) and gastric juice (150 cc.) was ultrafiltered. The ultrafiltrate (indicated by the letters I.M.U.) was given daily to the patient by mouth from June 13 to 22. In the third period, the alcoholic extract of meat (330 Gm.) was ultrafiltered. The ultrafiltrate (indicated by the letters A.E.M.U.) was mixed with gastric juice (75 cc.) and given daily to the patient by mouth from June 23 to July 25.

period of the present experiment. The products which can be formed by enzymatic splitting of the extrinsic factor must have still smaller molecules and must pass the ultrafilter even more easily than does the extrinsic factor. The second period of the present experiment shows clearly that these splitting products of the extrinsic factor cannot be demonstrated.

The third period shows that a much smaller amount of extrinsic factor, ultrafiltered *before* addition of the gastric juice, gives a marked therapeutic response. This positive result with the ultrafiltrate originating from ⅓ Kg. of meat contrasts with the insufficient response to the same amount of ultrafiltrate in experiment 7. This probably can be explained by the careful washing of the nonultrafiltrable rest and the ultrafilter in the present experiment, although individual quantitative differences in the therapeutic response to moderate amounts of effective mixtures cannot be excluded.

Comparison of the second and third periods of this experiment forms a strong argument against the hypothesis that an intermediate substance is formed by enzymatic splitting of the extrinsic factor. The possibility of insufficient formation of this hypothetic intermediate substance under the conditions of the experiment must be considered. This interpretation of the experiment is improbable because of the large amount of the original mixture (e. g., the known effective amounts of both extrinsic and intrinsic factor were doubled) and because of the total absence of even a small reticulocyte response, which may indicate administration of a therapeutic substance in an insufficient amount.

It seems to me that so many arguments against the existence of the hypothetic intermediate X substance have been shown that burden for the clinical proof of this hypothesis now lies on the other side.

The possibility that the combined action of gastric juice and duodenal juice could lead to transformation of the extrinsic factor into the liver factor was considered in the next experiment.

EXPERIMENT 16 (patient J. D.).—The 90 per cent alcoholic extract of meat (250 Gm.) was mixed with 50 cc. of gastric juice and 50 cc. of duodenal juice (obtained by duodenal tubage) and incubated for four hours. The incubated mixture was treated with 70 per cent alcohol, and the filtrate was administered daily to the patient by mouth for ten days, without any result. Afterward, injections of pernaemon gave a clearcut therapeutic result.

Comment on Experiment 16.—The combined effect of gastric and duodenal juice on the extrinsic factor did not lead to formation of an active principle soluble in 70 per cent alcohol, e. g., the liver factor. An analogous experiment has been performed by Castle, also with negative results.

The evidence of experiments 11 to 16 makes it probable that no reaction in vitro between the extrinsic factor and the intrinsic factor exists and that the essential interaction of these substances can take place only in the body. Castle has shown that a mixture of the extrinsic and the intrinsic factor is not active when the fraction of the mixture is strongly acid (p_H, 1.8 to 2.5); he concluded from this fact that the interaction between the extrinsic and the intrinsic factor probably takes

place in the gastrointestinal tract, because the inhibitive action of the acid reaction could not be maintained after absorption from the intestine. This fact, combined with the necessity of an in vivo phase for interaction of the extrinsic and the intrinsic factor, draws attention to the intestinal wall as the only possible place where these two conditions can be fulfilled. The experiments of Uotila [7] on the antianemic activity of the intestinal mucosa and of a progressive activity in the lower parts of the ileum are of special interest in this connection. The mode of action

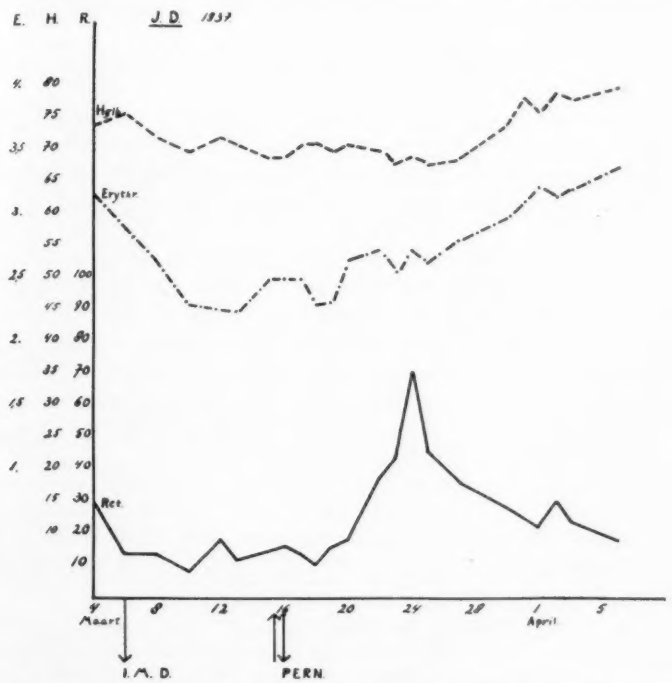

Chart 16 (experiment 16).—Incubated mixture of alcoholic extract of meat (250 Gm.) and gastric juice (50 cc.) was treated with 70 per cent alcohol (indicated by the letters I.M.D.) and given daily to the patient from March 6 to 16, 1937. Pernaemon was injected daily from March 16.

of the intestinal wall in this reaction will have to be determined by later experiments.

Parenteral application of the extrinsic factor alone or in combination with gastric juice is now under investigation. Small quantities of different active fractions of the meat extract have been injected into healthy

7. Uotila, U.: Acta med. Scandinav. **95**:415, 1938.

adults and into some patients with pernicious anemia, without effect on blood formation. Injection of greater quantities has been inhibited by severe local irritation; the separation of the irritating substance from the active principle is now being studied.

SUMMARY

A study of the properties of the extrinsic factor in meat has been made.

The extrinsic factor was present in a 70 to 80 per cent alcoholic extract of meat.

Fats and lipoids could be removed from this extract by ether extraction without loss of activity.

The extrinsic factor present in the extract passed through an ultrafilter.

A fraction of the extrinsic factor (less than 50 per cent) was present in the precipitate obtained by saturation of the extract with ammonium sulfate.

An analysis of Castle's reaction has been carried out.

The alleged formation of the antianemic liver factor in the incubated mixture of meat and gastric juice was investigated. The liver factor could not be demonstrated by treatment of the incubated mixture with 70 per cent alcohol and precipitation of the filtrate with 96 per cent alcohol; the precipitate was inactive when given by mouth or by injection.

Treatment of the incubated mixture with 70 per cent alcohol alone led to inactivation of the mixture.

Attention is drawn to the intestinal wall as the probable site of this reaction.

The conclusion is drawn that no reaction in vitro takes place between the extrinsic and the intrinsic factor and that only an in vivo reaction exists.

TRANSITORY INFILTRATION OF THE LUNG WITH EOSINOPHILIA

LÖFFLER'S SYNDROME

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AND
S. SAMUELSON, M.D.
JERUSALEM, PALESTINE

Since Löffler in 1931 first drew attention to a condition characterized by transitory infiltration of the lung and eosinophilia, increasing interest has been paid to this symptom complex by those engaged in the treatment of diseases of the lung. Löffler's syndrome consists of four cardinal signs which have been present in all the cases so far reported: signs of pulmonary disease on auscultation and percussion, the presence of a corresponding shadow in the roentgenogram, transience of the pulmonary signs and increase of the eosinophils in the blood.

One hundred and five cases have so far been reported, 51 by Löffler [1] himself. The importance of this condition, from the point of view of both differential diagnosis and prognosis, induces us to report a case which came under our observation.

The patient was a woman aged 25, of the asthenic type, 5 feet 8½ inches (174 cm.) tall and weighing 126 pounds (57 Kg.). After a long-drawn-out attack of bronchitis six years before, she had been subject to repeated attacks of catarrh of the air passages and bronchial asthma (particularly when the relative humidity was high or when she was in an atmosphere laden with tobacco smoke). No allergy of exogenic nature was demonstrable. Roentgen examination of the lungs on several occasions in recent years had shown them to be in normal condition. The blood picture and the sedimentation rate were normal. The heart and the circulatory system were normal. The blood pressure was 105 systolic and 80 diastolic (in the special climatic conditions of Palestine, which have a marked effect on the circulation, a single reading is of no great significance and cannot be compared to a like observation in Europe).

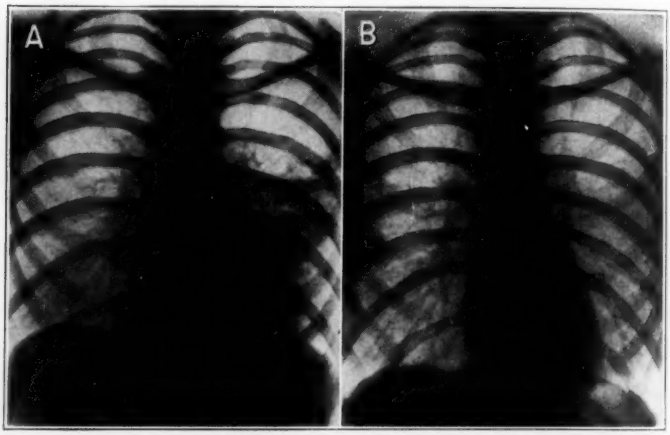
Nov. 8, 1937: The patient felt ill. Her temperature (axillary) was 100 F. There was pain on the left side of the chest on coughing. Over the middle of the left clavicle there was a gland the size of a plum, fairly hard and painful to the touch; palpation brought about a fit of coughing. On the left side below the clavicle and in the corresponding area posteriorly an area was noted as large as the palm of the hand, with decreased resonance, diminished breath sounds and a

1. Löffler, W.: (*a*) Zur Differential-Diagnose der Lungeninfiltrierungen: II. Ueber flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. d. Tuberk. **79**:368-382, 1932; (*b*) Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr. **66**:1069-1078 (Nov. 7) 1936.

few fine crepitations, surrounded by an area of bronchial breathing. There was no asthma. The cough was not productive. The clinical diagnosis was infiltration in the upper lobe of the left lung. The differential diagnosis was incipient phthisis (?).

November 9: The gland was the size of an almond but softer and still tender to touch. The temperature was normal. There was no change in the lung. Roentgen ray examination showed lateral to the left hilus a triangular shadow consisting of small patches which still enabled the structure of the lung to be made out. The diaphragm moved well. The phrenicocostal sinus was clear. The roentgen diagnosis was infiltration in the middle field of the left lung (fig. *A*).

November 10: The condition was unchanged. The blood picture and sedimentation rate are given in table 1. The diagnosis was Löffler's syndrome.



Roentgenograms of patient with Löffler's syndrome. *A* (Nov. 9), infiltration in the middle field of the left lobe. *B* (Nov. 25), no sign of the infiltration.

November 11: There was no change in the pulmonary condition. The gland was no longer palpable, but there was slight pain on pressure. There was slight pain on the left side of the chest on deep inspiration and on coughing.

November 13: The pulmonary condition was still demonstrable. There was a dry cough.

November 14 to *November 16:* No change was noted.

November 17: Diffuse bronchitis developed overnight, affecting both lungs. There were moist rales. No rise in temperature took place. Roentgen examination showed no sign of infiltration apart from a small area in the lateral part of the left middle field. The diagnosis of Löffler's syndrome was confirmed.

November 19: The bronchitis was disappearing. There was clear, gelatinous, tenacious sputum, containing few cells, no eosinophils, no red cells and no helminth eggs.

November 22: In the lungs no abnormalities were noted. The patient felt well and resumed her office work.

November 25: On roentgen examination there was no sign of infiltration of the left upper lobe (fig. *B*).

Table 1 gives the results of examinations of the blood during the period under observation. Examination of the stools on several occasions failed to reveal the presence of either worms or eggs.

The findings and the course of the disease—the mild symptoms and the marked objective appearances, the shadows in the roentgenogram of the lung, the transitory nature of the pulmonary condition and the eosinophilia—led us to conclude that we were dealing with a case of Löffler's syndrome.

A statistical survey of the cases hitherto reported in the literature is given in table 2.

It is to be regretted that detailed information is provided in only a quarter of the total number of cases reported. It would be desirable

TABLE 1.—*Results of Examination of the Blood*

Date	Red Blood Cells per Cu. Mm.	Hemoglobin, %	White Cells per Cu. Mm.	Basophils, %	Eosinophils, %	Neutrophils: Band Form, %	Neutrophils: Segmented, %	Lymphocytes, %	Monocytes, %	Sedimentation Rate, Mm.
11/10	3,800,000	70	9,850	1	11	3	55	27	3	16
11/11	.....	..	.....	0	22	4	43	26	5	..
11/13	.....	..	10,500	0	12	3	65	15	5	..
11/14	.....	..	9,575	0	18	4	50	23	5	..
11/15	.....	..	8,925	1	20	2	56	19	2	..
11/16	.....	..	9,950	0	18	2.5	52.5	22	5	..
11/17	.....	..	14,800	0	18	2.5	65.5	11.5	2.5	..
11/19	.....	..	.....	1.5	21	3	43.5	29	2	..
11/24	4,620,000	80	6,675	0	12	0	45	38	5	9
11/27	.....	..	8,300	1	8.5	0	51	31	8.5	5

from the point of view of systematic study were physicians to follow a scheme in taking histories which would provide information on: (1) age, (2) sex, (3) season and climate, (4) site of disease, (5) symptoms, (6) clinical signs, (7) roentgen observations, (8) blood picture, (9) sputum and stool, (10) duration of the disease and (11) possible etiologic factors. Such histories would make clinical classification possible.

It is not surprising that this condition was not defined earlier, for it is only in the last decade, when for social and hygienic reasons large numbers of examinations have been made in outpatient departments and clinics, that it has been possible to carry out observations which enabled Löffler to define this syndrome as a pathologic entity. The condition is usually so mild that the patient is rarely driven to consult a doctor. The signs, however, are so alarming, from the point of view of differential diagnosis and therapeutic measures undertaken, and so uniformly clear and sharply defined, that Löffler's syndrome has taken its place in the field of special pathology.

The absence of anatomic or histologic observations which might throw a light on the pathologic process is due to the fact that in all the cases hithero observed the condition has ended in resolution.

TABLE 2.—*Summary of Cases of Löffler's Syndrome Reported in the Literature*

Author	Number of Cases	Sex		Age		Site of Infiltration			Supposed Cause	Country, Season	Comment
		M	F	Adults	Children	Right	Left	Both			
Löffler [1].....	51	34	17	51	..	8	1	2	Tuberculid (all)	Switzerland; July, Aug.	Outpatients, 1931-1936
Geiger [11a]....	15	..	..	6	9	..	..	..	Undecided; 9 patients exposed to tuberculosis	Switzerland; May-Aug.	Tuberculosis dispensary; routine examinations 1933-1936
Oeri [11b].....	5	..	..	5	..	..	..	..	Coincidental tuberculosis	Switzerland; spring	Basel, sanatorium, 120 beds
Wild [6].....	14	..	..	—	14	..	..	..	Not stated; ascaris on 4 occasions	Switzerland; June-Aug.	Routine examinations in 2 elementary school classes
Jeanneret et Famé [11c]	3	..	..	3	..	3	..	..	?	Switzerland; ?	
Steiger and Rohner [2]	1	1	..	1	..	..	1	..	Allergy	Switzerland; March	Personal observation (H. R.) 1936
Hansson [8]....	1	..	1	1	..	..	..	1	Allergy	Sweden; May-Aug.	Relapse in bronchial asthma, 1933, 1934
Rossel and Hourlet [9]	2	1	1	2	..	2	..	(2)	Allergy	Switzerland; June, July	Both began on right side, then also left side; 1937
Leitner [11d]...	8	..	..	8	..	7	1	..	?	Switzerland; winter	Davos, sanatorium, 120 beds
Cohen [11e]....	1	..	..	1	..	..	..	..	Allergy	France; summer	Migraine patient
Viersma [10]...	2	1	1	2	..	1	1	..	?	Holland; April, July	
Freund and Samuelson	1	..	1	1	..	..	1	..	Allergy ?	Palestine; autumn	Relapse of bronchitis and bronchial asthma; 1937

As for etiologic factors, there is little divergence of opinion among observers. Steiger and Rohner [2] and Engel [3] differed from the majority

2. Steiger, J., and Rohner, H.: Flüchtige Lungeninfiltrierungen mit Eosinophilie, Deutsches Tuberk.-Bl. **11**:154-158 (June) 1937; in discussion on Löffler.[1b]

3. Engel, D.: Anaphylaktisches Frühjahrsödem der Lunge. Eine pseudoepidemische Erkrankung, Med. Klin. **2**:1466 (Nov. 8) 1935; Ueber eine eigenartige anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87**:239-250, 1935.

in speaking of an "epidemic incidence" ; but as there is no foundation for this belief from an epidemiologic point of view, the statement may be ignored. Engel in China and Koino [4] in Japan stated the belief that they could trace a direct connection with external factors. Engel observed a series of cases during the season when the privet was in blossom and regarded the condition as an anaphylactic reaction caused by breathing privet pollen. No such specific connection was established in Europe.

It may here be mentioned that Dickson [5] has recently described the coccidiomycosis syndrome, with details of its pathogenesis. He described the clinical and roentgen appearance of the lung in the acute stage, and this is identical with that of Löffler's syndrome. It seems probable that the observations of Engel, Koino and Dickson represent similar reactions to different antigens.

In this connection, some theoretic interest attaches to the experimental observations of Koino on the relation between the wanderings of ascaris larvae in the human body and the occurrence of pneumonia. But we agree with Löffler that under natural conditions when the infection is not as massive as it was in Koino's personal experiment, milder conditions may appear which may well fall into our category. Wild's [6] observations support this; he alone among all other observers found ascariasis in 4 of a total of 14 cases reported (table 2).

Wieland's [7] suggestion that climatic influences should be borne in mind is worth noting; he stated the opinion that indiscreet and prolonged exposure to the sun may lead to transient congestive conditions in particular areas of the lung. But in our opinion that plays only an exciting and not an etiologic role.

All writers, however, who have dealt with the etiology of Löffler's syndrome are agreed that allergic phenomena play a decisive part in its pathogenesis. Löffler himself, who has made the fullest study of the largest series of cases investigated and regarded the "transitory infiltration with eosinophilia" as a microbid or frequently as a tuberculid, based his opinions on the original classic conception of allergy in its narrower sense. Whether the preponderating amount of material on tuberculosis discussed by Swiss writers has not tended to affect the figures will be decided when the results of observation in other countries are known. In the present state of knowledge one should avoid analyzing the etiologic factors of each reported case and refer to the

4. Koino, S.: Japan M. World **2**:11, 1922; cited by Löffler.[1b]

5. Dickson, E. C.: Coccidiomycosis, J. A. M. A. **111**:1362-1365 (Oct. 8) 1938.

6. Wild, in discussion on Löffler.[1b]

7. Wieland, E., in discussion on Löffler.[1b]

details given in the original published observations (Löffler, Steiger and Rohner, Hansson,[8] Rossel and Houriet,[9] Viersma[10] and others[11]).

In all cases hitherto reported the condition has run such a mild course that the question of specific therapy has not arisen.

It is our opinion that Löffler's syndrome is a clinical entity the definition of which is particularly important from the point of view of prognosis and treatment. We believe, with Rossel and Houriet, that we are dealing with a condition in which a variety of causative factors may produce this clearly defined symptom complex in a suitable case.

There appears to be no doubt that the clinical observations in the lung which indicate infiltration, whether cellular, exudative or atelectatic (as in our case), can always be established by careful percussion and auscultation. This should be an indication—independent of the course and intensity of the condition—for examination of the blood (leukocyte count and blood film, on a thick drop for a rough estimate of eosinophils) and roentgen examination. The diagnosis of this symptom complex is of more than mere academic interest, mild as its course and results are. Its recognition is of the utmost practical importance from the point of view of differential diagnosis from pulmonary tuberculosis, as may be noted in the case reported by Dickson, in which a mistaken diagnosis of tuberculosis was made, with all its attendant consequences.

SUMMARY

Observations are made on Löffler's syndrome, and a further case is reported.

The importance of the recognition of Löffler's syndrome lies in its differential diagnosis from tuberculosis, for it is characterized by similar clinical observations and roentgenologic appearance of the lungs.

Examination of the blood which reveals eosinophilia points to the possibility of a "transitory infiltration of the lung with eosinophilia" (Löffler's syndrome). Further clinical and roentgenologic observation confirms this and differentiates the condition from tuberculosis.

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SUBACUTE COR PULMONALE

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Admitting the rarity of occurrence, Brill and Robertson [1] called attention to what may prove to constitute a clinicopathologic entity, namely, subacute cor pulmonale. The features of this condition, according to their case report and to 2 similar ones that they were able to find in the literature, differ rather sharply from those of the acute and chronic forms of cor pulmonale. The acute form, confined practically to pulmonary embolism, is rarely associated with right ventricular hypertrophy. The chronic primary type [2] includes pulmonary stenosis and insufficiency, pulmonary endarteritis, organic tricuspid insufficiency, mitral stenosis, diffuse pulmonary fibrosis [3] and pulmonary emphysema. In the latter group the clinical course is usually protracted, right ventricular hypertrophy and dilatation are usually marked, and the cause is often clinically apparent. The subacute variety is characterized by a fairly rapid (nine days to two months) development and termination of signs and symptoms of strain of the right side of the heart in persons giving no history of previous cardiac or pulmonary disease, by moderate enlargement and dilatation of the right side of the heart and, further, by being undiagnosed.

In the case presented by Brill and Robertson and in the 2 abstracted by them (Krutzsch [4] and Schmidt [5]) the right ventricular strain was due to carcinomatous metastases to the pulmonary arterioles and to the peribronchial lymphatics, with secondary arteriolar thromboses. The

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From the Department of Pathology of St. Luke's Hospital.

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2. Thompson, W. P., and White, P. D.: The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, Am. Heart J. **12**:641-649 (Dec.) 1936.

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4. Krutzsch, G.: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. f. Path. **23**:247-271, 1920.

5. Schmidt, M. B.: Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.

primary tumors in all instances were unrecognized gastric carcinomas. In 2 of these cases diffuse ramifying white threads representing tumor were seen macroscopically coursing through the exposed surfaces of the lungs. No such observations were noted in the third instance. Adequate clinical explanation of the cor pulmonale was lacking in all 3.

The following case presents a condition that clinically and pathologically readily fits that recently designated as subacute cor pulmonale. The only differing point in this instance is that the primary carcinoma arose in the breast rather than in the stomach.

REPORT OF A CASE

History.—Mrs. J. N., a white woman aged 65, entered St. Luke's Hospital on Jan. 21, 1939 complaining chiefly of shortness of breath. Nineteen months prior to this hospitalization she had had a radical amputation of her right breast because of carcinoma. This operation was performed elsewhere. One month after this procedure she stated that she first noticed "neuritis" in her left leg. Mild intermittent pain was noted occasionally to the time of admission. Otherwise her health had been good until three weeks previously, when she first noticed shortness of breath which was not brought on by exertion. Since that time this symptom had been severe and constant. She had had no cough or pain in the chest. There was no history of tuberculosis or pneumonia.

Course.—Her temperature was 36.9 C. (98.4 F.) and her pulse rate 110 per minute. The systolic blood pressure was 140 mm. of mercury and the diastolic 80 mm. The elongated radical mastectomy scar on the right side appeared well healed, and there was no evidence of recurrent tumor. There was no cyanosis. Examination of the chest gave essentially negative results, though a few fine rales were heard over the base of the right lung. The heart rate was fast (110) but regular. No cardiac murmurs were heard. The abdomen and extremities were essentially normal. The urine was normal. Examination of the blood showed moderate anemia: 3,870,000 red cells per cubic millimeter and 11 Gm. of hemoglobin per hundred cubic centimeters. There were 79 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 5 per cent monocytes and 1 per cent basophils. The Kolmer and Kline tests of the blood gave negative results. At this time it was felt that the patient had an intrathoracic metastatic carcinoma, although there were no clinical signs indicative of such a diagnosis. Shortly after entry a roentgenogram of the chest, read by Dr. C. C. Fulmer, showed the heart to be of borderline size, with a full right margin (fig. 1). The aortic arch was normal. Diffuse peribronchial thickening and some little evidence of emphysema were noted. Calcification was observed in both hilar zones. There was no roentgenologic evidence of metastatic tumor in the chest. A roentgenogram of the spine and pelvis prior to hospitalization showed no metastases. In spite of the patient's dyspnea she was fairly comfortable during the next few days. Her temperature remained within normal limits, and her respiratory rate was from 22 to 24 per minute. The pulse rate remained consistently elevated, ranging from 100 to 130 per minute. On the sixth day in the hospital (twenty-seven days after the onset of symptoms) her moderate dyspnea suddenly became severe, and she complained of pain in the left

side of the chest. She had no cyanosis. It was felt that she probably had a coronary occlusion. At this time her red blood cells numbered 4,430,000 per cubic millimeter. The hemoglobin amounted to 13.3 Gm. per hundred cubic centimeters. The white blood cells numbered 13,300 per cubic millimeter. The differential count showed 77 per cent polymorphonuclear cells, 17 per cent lymphocytes and 6 per cent monocytes. She died before an electrocardiogram could be taken.

Gross Observations at Necropsy.—The external examination of the body showed no abnormalities other than a slight symmetric increase in the anterior-posterior diameter of the chest; there was no dependent edema and no evidence of recurrent

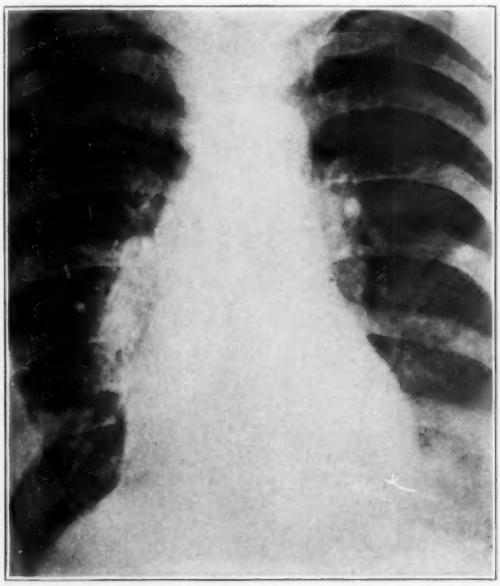

Fig. 1.—Roentgenogram of the chest, showing the configuration of the heart (three days before death).

or metastatic tumor. The general nutrition of the body appeared fairly good. Aside from a few isolated, discrete metastatic carcinomatous nodules in the under surface of the left lobe of the liver (weight 1,310 Gm.), there were no noteworthy changes in the abdominal organs or tissues. There was no evidence of a nutmeg condition of the liver. Both pleural spaces were obliterated by diffuse fibrous adhesions, but there was no evidence of tumor. These adhesions were separated with ease. Sagittal sections of each lung revealed fluffy, pinkish gray, air-containing presenting surfaces in which consolidation and tumor were not recognized. The right lung weighed 370 Gm. and the left 290 Gm. The maximum transverse diameter of the heart measured 13 cm. Eleven centimeters of this anterior presenting surface was formed by the right ventricle and auricle, the former chamber

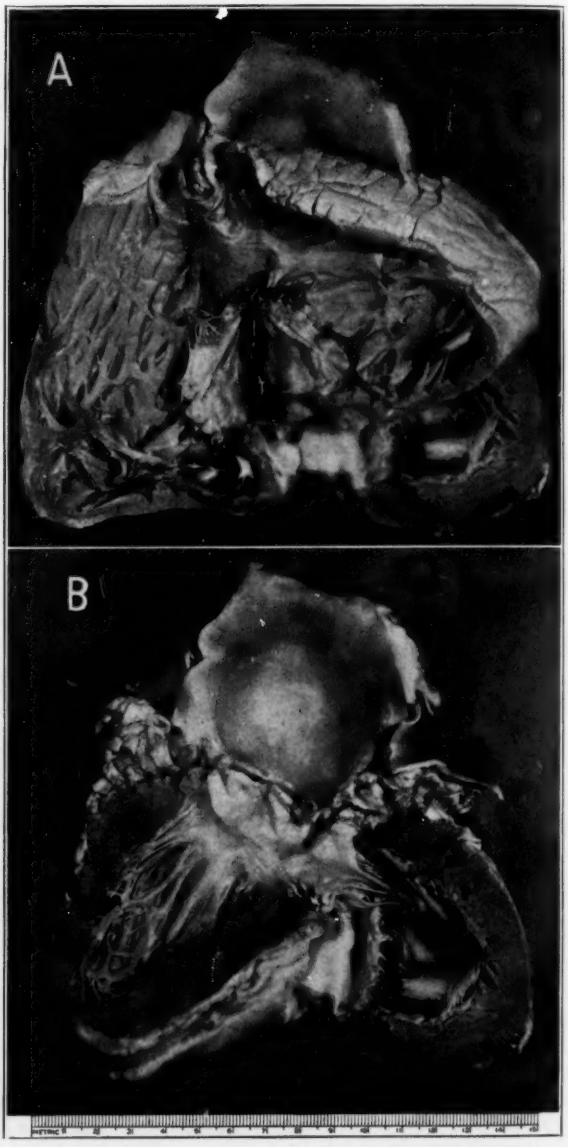

Fig. 2.—The heart, showing (*A*) the hypertrophy and dilatation of the right ventricle and (*B*) the smallness of the left ventricle and its trabeculae carneae.

Fig. 3.—*A*, emboli of tumor cells in the dilated arterioles (× 117). *B*, carcinoma cell plugging of prearteriolar pulmonary arteries, with secondary thrombosis (× 117).

constituting a predominant share. The pulmonary conus bulged perceptibly. In contradistinction to the small left ventricle, the right was dilated and hypertrophied (fig. 2). Thickening of the trabeculae carneae and of the papillary muscles was evident, and the former structures were flattened against the right ventricular wall. The myocardium of this chamber measured 6 mm. in thickness at the base and from 3 to 4 mm. at the apex. The wall of the left ventricle was 1.5 cm. in thickness at the base and 1 cm. at the apex. The trabeculae carneae

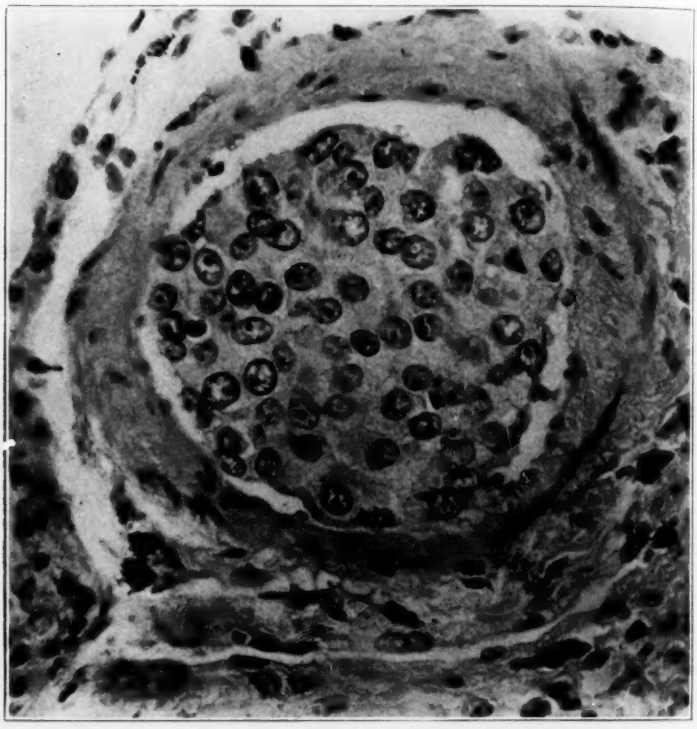

Fig. 4.—The carcinoma cells. Particles of coal dust lie in the perivascular lymphatics. (× 479).

here were much smaller than those on the right side of the heart. The cardiac valve rings measured as follows: pulmonic, 7 cm.; aortic, 7 cm.; mitral, 9 cm., and tricuspid, 12.5 cm. There was no evidence of valvular disease or of coronary arteriosclerosis or occlusion. The pulmonary arteries, aorta and cardiac septums were essentially normal. The heart weighed 325 Gm. During the removal of the brain the frontal bone was found to cut with decreased resistance and to be soft and porous. It measured 1.3 cm. in thickness. The meninges were normal. There was no evidence of edema or tumor in the brain or brain stem. The organs

of the neck, the spinal medulla and the vertebral column were not examined. The cause of death was attributed to the cor pulmonale, which in itself was unexplained until the microscopic sections were seen.

Microscopic Observations at Necropsy.—Microscopic sections of the lungs revealed the small divisions of the pulmonary arteries and the arterioles to contain solid nests of tumor cells (fig. 3), which in most instances completely filled and plugged the vessel lumens. In certain of the vessels part of the lumen contained thrombi in addition to the carcinoma cells (fig. 3*B*). A few such clots were old and organized. None of the vessels exhibited any evidence of intimal thickening. The individual tumor cells (fig. 4) were closely packed and diffuse in arrangement and possessed rather large, round to oval, vesicular, slightly hyperchromatic nuclei. Nucleoli were prominent. Rare mitotic figures were present. These cells showed no evidence of invading the encircling walls of the blood vessels and were never seen in the capillaries, peribronchial lymphatics or lung tissue proper. Atrophy, with occasional rupture of an alveolar wall, was noted to a slight extent. Decalcified sections of the frontal bone revealed small nests of carcinoma cells present in young fibrous connective tissue stroma existing between degenerating bone trabeculae. These cells were identical to those present in the pulmonary arterioles and arteries.

Sections of the hypertrophic right ventricle revealed some moderate broadening of individual myocardial cells, with some squaring and hyperchromatism of the contained nuclei.

Anatomicopathologic Diagnoses.—Pertinent diagnoses were: (1) hypertrophy and dilatation of the right ventricle (subacute cor pulmonale); (2) embolism of the pulmonary arterioles and small arteries by tumor cells, with recent and organized thrombosis; (3) old (nineteen months) radical mastectomy on the right side, for carcinoma; (4) secondary carcinoma of the liver and frontal bone, and (5) slight pulmonary emphysema.

COMMENT

The only other reference in the literature to the term subacute cor pulmonale is one by Maddox,[6] who, apparently unaware of Brill and Robertson's previous report, presented 2 clinical cases that he chose to classify under this title. The salient features of these cases are as follows:

A 42 year old woman with a history of long-standing hypertension was hospitalized with the complaints of pain in the chest (nine days), cough and cyanotic lips and fingers (five days). These symptoms and signs were such as to warrant an entry diagnosis of spontaneous pneumothorax. With the taking of digitalis she improved, and within eight days the roentgenographic transverse diameter of her heart changed from 14.4 cm. to 12 cm. During this hospitalization her blood pressure ranged between 180 and 150 systolic and 110 to 90 diastolic.

The second patient was a 49 year old man who had complained of asthma for many years, expectorant cough (six years), edema of the ankles (three weeks),

6. Maddox, K.: Subacute Cor Pulmonale, M. J. Australia **1**:18-21 (Jan. 7) 1939.

dyspnea on exertion and cyanosis on hospitalization. His blood pressure was 180 systolic and 110 diastolic. The roentgenologic transverse diameter of his heart changed from 15.7 cm. on the fifth day in the hospital to 13.1 cm. two weeks later. After five weeks his cyanosis cleared, but the dyspnea remained.

If the criteria for the classification of subacute cor pulmonale are adhered to,[1] it is evident that Maddox' cases are of a different condition. Judging from his report it seems that they probably represent subacute bouts of right ventricular strain as a phase (initial?) of what may prove to be chronic cor pulmonale, secondary to a failing left ventricle in the hypertensive case and primary in the case of emphysema. Both of the patients had an antecedent history of cardiopulmonary disease, and both recovered.

Death in the case that I presented was due to failure of the right side of the heart, secondary to obstruction and obliteration of the finer pulmonary vascular bed, which in turn was due to embolism of the blood stream by carcinoma cells. The hypertrophy and dilatation of the right ventricle were not recognized clinically, and their cause was not understood at autopsy. After the examination of the microscopic sections of the lungs, the gross specimens were looked over more carefully. Then one was able to see a few pinhead-sized white dots throughout the lungs. They were always at least 2 or 3 cm. from one another. These visible lesions represented tumor cell emboli in the smaller pulmonary arteries. The emboli in the arterioles were not visible. The metastasis in the frontal bone and the few nodules in the liver were incidental in relation to the cause of death. In view of the moderate but definite right ventricular hypertrophy, as well as occasional well organized thrombi in certain of the arterioles, it appeared likely that pulmonary obstruction and hypertension existed before the onset of the patient's symptoms, twenty-seven days before death. The right side of the heart, in spite of the existence of dyspnea for this time and the progressive increase of the vascular obstruction, must have compensated to a moderate degree until near the end, as the liver at autopsy showed no gross or microscopic evidence of injury.

This case makes only the fourth published case of subacute or pulmonale. In all instances the patients have been free of antecedent signs or symptoms of cardiorespiratory disease. The clinical course from the onset of symptoms to the time of death has varied from nine days to two months. The obstruction to the right side of the heart was due to embolism of the pulmonary arterioles by tumor cells, to metastases to the perivascular lymphatics or to both, with secondary thromboses. In 3 cases the primary carcinoma was in the stomach, and in another it

was located in the breast. It is thought that this condition is more common than it has so far proved to be, but the question of frequency awaits further reported examples.

SUMMARY

An example of an instance of subacute cor pulmonale is presented. Death was due to fairly rapid obstruction (clinically recognized twenty-seven days) of the pulmonary arterioles and prearteriolar arteries, with ensuing failure of the right side of the heart. The vascular obstruction was due to emboli of small carcinoma cells arising from a primary carcinoma of the breast, for which radical mastectomy had been performed nineteen months previously.

STUDIES OF THE BLOOD IN CONGESTIVE HEART FAILURE

WITH PARTICULAR REFERENCE TO RETICULOCYTOSIS, ERYTHROCYTE FRAGILITY, BILIRUBINEMIA, UROBILINOGEN EXCRETION AND CHANGES IN BLOOD VOLUME

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That the total circulating blood volume is increased during congestive heart failure [1] and is decreased after recovery [1b,c] has been convincingly demonstrated. Knowledge is incomplete, however, in regard to the mechanisms involved in creating and in disposing of the increased circulating volume of erythrocytes and plasma during the different stages of congestive failure. In the present investigation the reticulocyte percentage, red cell fragility, serum bilirubin and urinary and fecal excretion of pigment were studied in a series of patients at intervals during the height of, and recovery from, congestive heart failure; these findings were related to the observed changes in blood volume and clinical status.

METHODS

The total blood volume, plasma and circulating red blood cell mass were ascertained by means of Evans blue dye and the photoelectric colorimeter, as described by Gibson and Evans [2] and Gibson and Evelyn.[3] Measurements were

The study was aided in part by a grant from the Proctor Fund of Harvard Medical School.

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From the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

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made soon after the patient's admission to the hospital and subsequently at four or eight day intervals (tables 1, 2, 3, 4 and 5) when he was in the fasting state. All blood samples were drawn, without stasis, from a cubital vein. Hematocrit measurements were made in Rourke-Ernstene sedimentation tubes [4] with a mixture of potassium and ammonium oxalate as the anticoagulant. The total red cell mass was calculated from the average of three hematocrit measurements, taken at the beginning, in the middle and at the end of the plasma volume estimation. The initial reading was recorded on the charts and tables, whereas the average value, which was lower by from 1.0 to 3.0 per cent of cells, was used in the calculation of the total blood volume. The fragility of the red cells to hypotonic solutions of sodium chloride [5] was observed immediately after withdrawal of the samples of blood. This procedure utilizes a constant volume of sample and volume of solution of sodium chloride, and each experiment was done at the same temperatures and intervals. The blood was collected without stasis and with a constant concentration of anticoagulant. All readings were made by the same observer.

The venous pressure [6] and the quantity of bilirubin in the serum, as measured by the photoelectric colorimeter,[7] were estimated at the time of the measurement of blood volume. The arm to tongue circulation time was measured with either sodium dehydrocholate or calcium gluconate; the same substance was used in all tests on any given patient.

The urinary and fecal biliary pigments were estimated by the method of Watson,[8] in which all urobilin is reduced to urobilinogen and measured colorimetrically. Twenty-four hour collections of stools and urines were made separately each morning at 7 a. m. The urobilinogen content of the urine was measured immediately. The stools were kept in waxed cardboard containers in the refrigerator. Every fourth day, except for a longer or shorter period as indicated on the tables, the stools of the previous four days were weighed and thoroughly mixed and two accurately weighed samples taken for analysis. The values of the two samples agreed within plus or minus 10 per cent of their average when the fecal excretion was over approximately 75 mg. of urobilinogen per day, and within plus

2. Gibson, J. G., and Evans, W. A.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectro-Photometer, J. Clin. Investigation **16**:301, 1937.

3. Gibson, J. G., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to Photoelectric Microcolorimeter, J. Clin. Investigation **17**:153, 1938.

4. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**:545, 1930.

5. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, J. Lab. & Clin. Med. **20**:1122, 1935.

6. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

7. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481, 1937.

8. Watson, C. J.: Studies of Urobilinogen: I. Improved Method of Quantitation, Am. J. Clin. Path. **6**:458, 1936.

or minus 20 per cent when the daily excretion was less. The average of the duplicate analyses appears in the tables. Reticulocyte counts were done on smears made on brilliant cresyl blue stain and counterstained with Wright's stain. One thousand red blood cells were examined on each of two preparations. If the difference in the reticulocyte percentage exceeded 0.3 per cent, fresh preparations were obtained and examined.

MATERIAL

Five ward patients with uncomplicated chronic congestive heart failure were studied in detail. Fifteen investigations were initiated, but ten were discontinued because of diabetic acidosis, uremia, pulmonary infarcts with hemoptysis, bronchial asthma or death. Four of the 5 completely studied patients showed peripheral evidences of congestive heart failure, and 1 patient had predominantly left ventricular failure. Studies were begun within a few hours after the patients were admitted to the hospital and extended over periods ranging from seventeen to forty-one days. The usual medical measures were utilized in the treatment of these patients.

REPORT OF CASES

CASE 1.—B. L., a 58 year old man, was admitted to the hospital on Nov. 22, 1938. The patient first noticed increasing dyspnea on exertion three years before his admission. A chronic cough, productive of mucopurulent sputum, had been present for over twenty years. In the year preceding admission there had been exacerbation of the cough with orthopnea, dyspnea on slight exertion and slight edema of the ankles.

On admission the patient was extremely cyanotic and moderately orthopneic and dyspneic; he had a frequent harassing cough, productive of tenacious mucopurulent material. The heart was markedly enlarged to the right and to the left, with regular sinus rhythm. Blood pressure was 140 systolic and 90 diastolic. The lungs were filled with coarse rhonchi, and there were moist rales at both bases. The liver was tender and extended two fingerbreadths below the costal margin. There was no ascites or sacral edema and but minimal edema of the ankles. The nonprotein nitrogen of the blood was 40 mg. per hundred cubic centimeters.

Course.—The patient rapidly lost weight after mercurial diuresis. The cough, orthopnea, dyspnea and edema decreased, as did the cyanosis. Complete digitalization was attained by the fourth day, when marked clinical improvement was already noted. However, the patient at no time became entirely free of orthopnea. He continued to gain weight during rest in bed and required frequent administration of mercurial diuretics. He was discharged on Jan. 1, 1938, markedly improved but still with slight congestive failure.

CASE 2.—J. N., a 62 year old man, was admitted to the hospital on Oct. 15, 1938. The patient complained of frequency of urination and nocturia of fifteen years' duration. Six months previous to the present admission, edema of the ankles and rales at the bases of the lungs were noted and successfully treated with rest in bed and the administration of digitalis. Three months before the present admission there was an episode of paroxysmal nocturnal dyspnea. Following this there were increasing dyspnea on exertion and orthopnea. The latter caused the patient to sleep in the sitting position for several weeks preceding admission. Edema of the ankles, first noted two months previously, became more marked and finally was not relieved by rest in bed.

Physical examination revealed a well nourished white man, sitting upright in bed, slightly dyspneic and markedly orthopneic. There was no cyanosis. The patient was not well orientated, and comprehension was poor. The heart was enlarged and overactive; the pulse was regular in rhythm. The blood pressure was 170 systolic and 98 diastolic. There were a small right hydrothorax and a few moist rales at the bases of both lungs. The liver was palpable three fingerbreadths below the costal margin. No other abdominal viscera were palpable, and no ascites

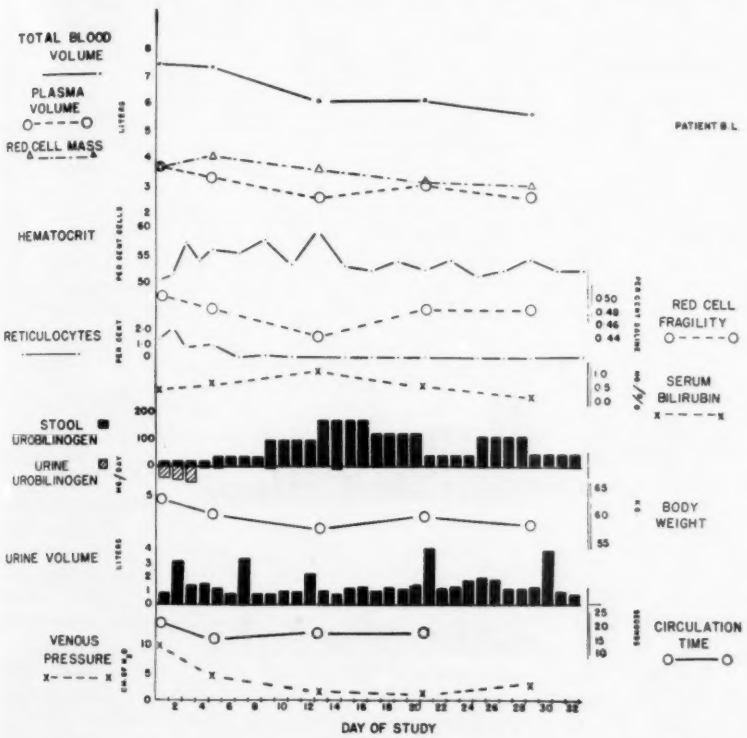

Chart 1.—Graphic presentation of findings in case 1, that of B. L., a 58 year old man, 162 cm. in height. The diagnoses were generalized arteriosclerosis, arteriosclerosis of the coronary arteries, congestive heart failure, chronic bronchitis and emphysema. (Normal calculated blood volume, 4,400 cc.)

was present. There was but minimal pretibial pitting edema. No prostatic enlargement was demonstrable. The urine contained no albumin and only occasional white blood cells. The nonprotein nitrogen of the blood was 36 mg. per hundred cubic centimeters.

Course.—The patient was digitalized and was given a salt-poor diet and a restricted fluid intake. By this regimen the frequency of urination and orthopnea were completely relieved. No pulmonary rales or edema of the ankles was

evident after the fourth hospital day. The patient was free of all signs and symptoms on the seventh hospital day, and on the nineteenth day he was allowed lavatory privileges. He was discharged on Nov. 5, 1938, at which time he was still free of all signs and symptoms of congestive failure.

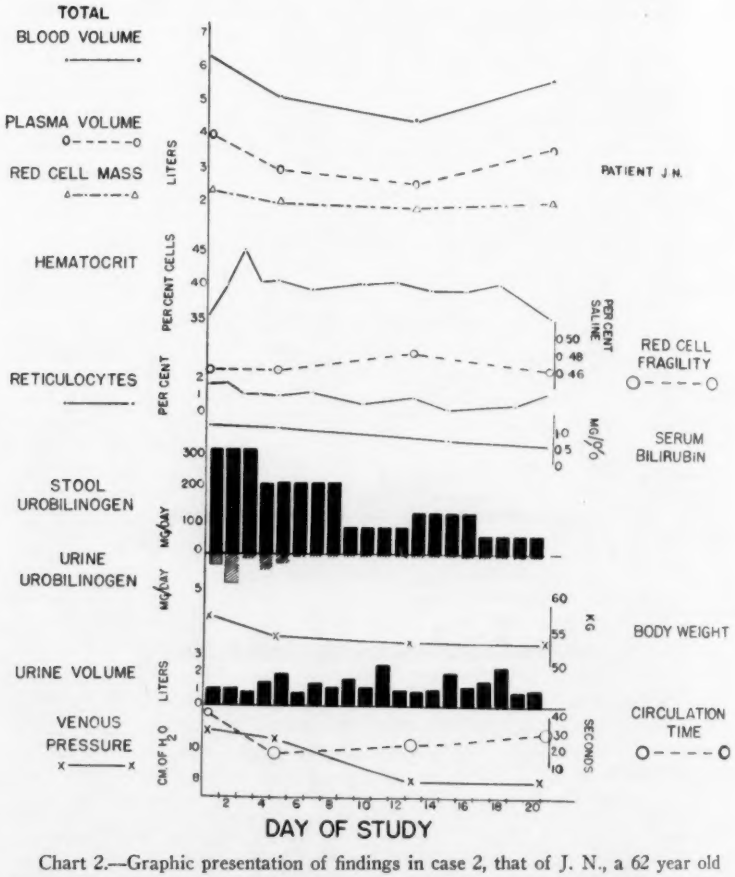

Chart 2.—Graphic presentation of findings in case 2, that of J. N., a 62 year old man, 160 cm. in height. The diagnoses were arterial hypertension, arteriosclerosis, arteriosclerosis of the coronary arteries, congestive heart failure and cystitis. (Normal calculated blood volume, 4,400 cc.)

Case 3.—J. G., a 53 year old woman, was admitted to the hospital on Feb. 15, 1938. The patient first noticed slight dyspnea on exertion six years before the present admission and shortly thereafter began to have episodes of paroxysmal nocturnal dyspnea. These increased in frequency as the dyspnea on exertion became more severe. A year later edema of the ankles made its first appearance,

and several months later the abdomen began to swell. The first admission to this hospital, three years previously, resulted in complete disappearance of cyanosis, orthopnea, paroxysmal dyspnea and edema. A return to normal activity, however, brought on a recurrence of dyspnea, both paroxysmal and on exertion, as well as edema of the ankles and swelling of the abdomen. In the year preceding the present admission the patient remained constantly in bed, was orthopneic and never became free of edema.

On admission the patient was cyanotic, moderately dyspneic and orthopneic. The heart was enlarged to the left; the pulse was regular and rapid. Blood pressure was 280 systolic and 140 diastolic. Coarse rales were heard throughout both lungs, and there was flatness at the left base posteriorly. The liver was palpable four fingerbreadths below the costal margin, and the abdomen contained a moderate amount of fluid. The lower part of the legs and the ankles, as well as the lower part of the abdominal wall, were edematous. The nonprotein content of the blood was 30 mg. per hundred cubic centimeters, and the total protein content of the blood was 6.8 per cent. Improvement was rapid as a result of mercurial diuresis and digitalization. The patient became free of edema and less orthopneic,but the cyanosis was still present when she was discharged from the hospital. In spite of a regimen of restricted fluid intake and oral diuretics, the repeated reappearance of edema of the ankles and rales in the lungs made frequent use of intravenous diuretics necessary. The patient was discharged to a hospital for patients with chronic diseases on March 28, 1938.

CASE 4.—W. W., a 59 year old man, was admitted to the hospital on Jan. 17, 1938. Three years before the present admission the patient first noticed dyspnea on exertion. This became increasingly more severe and was soon followed by swelling of the ankles. During the first six months of illness large amounts of fluid were removed from the chest at another institution. During the next two and a half years the patient was completely incapacitated because of dyspnea at rest, orthopnea and marked swelling of the legs. During that time he was admitted to this hospital on three occasions, once in 1936 and twice in 1937. In the month preceding the present admission, despite continued digitalis and repeated intravenous mecurial diuretics, the patient became more edematous and more dyspneic. A continual cough with blood-tinged sputum appeared, as did periods of severe transitory substernal oppression.

On admission the patient seemed at the point of death. There was marked cyanosis and orthopnea, and breathing was in short gasps. Frequent cough was productive of large amounts of foamy, blood-tinged fluid. The pulse was rapid, with regular sinus rhythm. The blood pressure was 155 systolic and 110 diastolic. The right and left pleural cavities were flat to percussion up to the midscapular region. The abdomen was distended and filled with fluid, and the edge of the liver was not palpable, but tenderness in the right upper quadrant extended down to the umbilicus. There was marked pitting edema of the legs and of the entire abdominal wall. The nonprotein nitrogen content of the blood was 37 mg. per hundred cubic centimeters.

Course.—Immediately on admission bilateral thoracentesis was performed and a diuretic administered intravenously. The patient was placed in an oxygen tent. Within the first three hours there was definite subjective and objective improvement. Measurement of the blood volume was made six hours after admission. On the third hospital day the patient was removed from the oxygen tent. With repeated diureses he rapidly became free of detectable edema. By the eighteenth

day he was free of all signs of congestive heart failure; there was no edema, demonstrable hydrothorax or ascites and no orthopnea or dyspnea. The patient was maintained at rest in bed, with no further mercurial diuretics or gain in weight, until his discharge from the hospital on March 13, 1938.

CASE 5.—D. N., a 59 year old woman, was admitted to the hospital on Oct. 5, 1938. The first admission to the hospital occurred five years previously for acute appendicitis. At that time there was no evidence of cardiac insufficiency, either by history or by physical examination. The patient remained perfectly well until three months prior to the present admission, at which time she noted pain in the right anterior portion of the chest, brought on by walking and disappearing with rest. Eight days before admission there was an episode of paroxysmal nocturnal dyspnea accompanied by wheezing; this had recurred nightly since that time. There were dyspnea on exertion, cough and generalized weakness of like duration. No swelling of the feet and no pain in the right upper quadrant of the abdomen was present.

On admission the patient was slightly cyanotic and orthopneic, but not dyspneic. There was no cardiac enlargement. Examination of the heart revealed regular sinus rhythm. The blood pressure was 170 systolic and 105 diastolic. Rales were present at the bases of both lungs posteriorly. The peripheral veins were not engorged, and the liver was not palpable. There was no pitting edema of legs or sacrum.

Course.—The patient was given phenobarbital and theobromine with sodium acetate, and digitalization was carried out for four days. There was no recurrence of paroxysmal dyspnea or of angina pectoris. The rales in the lungs gradually disappeared. Mercurial diuretics, given intravenously on two occasions, caused no loss of weight or increased urinary output. The patient was discharged from the hospital on Oct. 22, 1938, with no signs of heart failure.

RESULTS

Total Blood Volume.—The 4 patients (tables 1, 2, 3 and 4; charts 1 and 2) with peripheral evidences of congestive heart failure had initial blood volumes varying from 125 per cent to 223 per cent of the expected normal calculated values according to height and sex.[9] After clinical improvement, a decrease to normal calculated values in 2 patients and to 128 per cent and 196 per cent of normal in the other 2 patients was noted. One patient (table 5) with predominant left ventricular failure had a normal initial blood volume, with first a slight increase and then a slight decrease. One (table 2) had a distinct increase in total blood volume during the last few days of study, when he was allowed out of bed.

Changes in Red Blood Cell Volume and Plasma Volume.—The blood volume increase observed at the beginning of the study consisted of

9. Gibson, J. G., and Evans, W. A.: Clinical Studies of the Blood Volume: II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, J. Clin. Investigation **16**:317, 1937.

TABLE 1.—*Findings in Case 1 (B. L.).* Diagnoses: Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Heart Failure, Chronic Bronchitis and Emphysema*

Days of Study	Weight, Kg.	Total Blood Volume,† Cc.	Plasma Volume,† Cc.	Red Cell Mass,† Cc.	Hematocrit,† Per Cent Cells	Reticulocytes, Average Per Cent	Serum Bilirubin, Mg. per 100 Cc.	Urine Volume, Average Cc. per Day	Urinary Pigment, Average Mg. per Day	Fecal Pigment, Average Mg. per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm. of Water	Circulation Time,† Seconds	Clinical Findings
1- 4	63.5	7,400	3,700	3,700	50.4	1.2	0.3	1,490	2.0	19	0.50	100	21	Subsidence of cough and edema
5- 8	60.0	7,300	3,250	4,050	56.0	0.5	0.5	1,290	Trace	31	0.48	45	15	Loss of rales and cyanosis
9-12	57.7	.....	.....	.....	57.5	0.1	...	1,240	Trace	97	....	..	..	
13-16	57.2	6,050	2,540	3,510	59.0	0.0	1.0	1,050	Trace	138	0.44	20	17	
17-20	59.5	.....	.....	.....	52.0	0.0	...	1,212	0.0	119	....	..	..	Persistent orthopnea
21-24	59.5	6,120	3,000	3,120	52.0	0.0	0.4	2,071	0.0	38	0.48	15	17	
25-28	60.0	.....	.....	.....	51.0	0.0	...	1,490	0.0	108	....	..	..	Gaining weight at bed rest
29-32	58.2	5,650	2,655	2,995	54.0	0.0	0.2	1,753	0.0	38	0.48	30	..	

* The patient was a 58 year old man, 162 cm. in height. The normal calculated blood volume is 4,400 cc.
† These observations were made on the first day of each four day period.

TABLE 2.—*Findings in Case 2 (J. N.).* Diagnoses: Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Failure and Cystitis*

Days of Study	Weight, Kg.	Total Blood Volume,† Cc.	Plasma Volume,† Cc.	Red Cell Mass,† Cc.	Hematocrit,† Per Cent Cells	Reticulocytes, Average Per Cent	Serum Bilirubin, Mg. per 100 Cc.	Urine Volume, Average Cc. per Day	Urinary Pigment, Average Mg. per Day	Fecal Pigment, Average Mg. per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm. of Water	Circulation Time,† Seconds	Clinical Findings
1- 4	57.2	6,250	3,960	2,290	36.5	1.4	1.2	1,090	2.4	305	0.46	110	40	Loss of edema and rales
5- 8	54.5	5,020	2,990	2,030	41.7	1.2	1.1	1,275	0.8	210	0.46	105	17	Loss of orthopnea
9-12	53.0	.....	.....	.....	40.1	0.5	...	1,500	0.2	81	....	..	..	Free of all signs and symptoms of failure
13-16	52.7	4,450	2,610	1,840	41.9	0.6	0.7	1,250	0.2	125	0.48	80	22	
17-20	52.1	.....	.....	.....	38.0	0.4	...	1,400	Trace	58	....	..	..	Lavatory privileges
21	53.0	5,610	3,660	1,950	35.7	1.1	0.6	.....	...	..	0.46	80	27	Discharged symptom free

* The patient was a 62 year old man, 160 cm. in height. The normal calculated blood volume is 4,400 cc.
† These observations were made on the first day of each four day period.

increase in both the plasma volume and the red blood cell volume; the percentage changes in red cell volume and plasma volume were approximately equivalent. The initial hematocrit values ranged from 37 to 53 per cent cells for the entire group of cases. During the early fall in the total blood volume in the course of recovery, the plasma volume usually decreased to a greater extent than the red cell volume, as evidenced by increase in the hematocrit value. As the blood volume dropped further, the hematocrit value returned to its previous status. In the instance already mentioned (table 2) in which the blood volume showed a secondary rise, the increase was due chiefly to an increase in plasma volume.

Reticulocyte Findings.—For the 4 patients with peripheral evidences of congestive heart failure and increased blood volume the reticulocyte counts on admission to the hospital ranged from 1.2 to 2.7 per cent. During recovery the reticulocyte counts decreased for all of these patients to levels of 0.5 per cent or less. For 1 patient (table 2) in whom the blood volume increased when he was allowed up and about, the reticulocyte percentage increased slightly.

Fragility of the Erythrocytes.—The initial values for the fragility of the red blood cells ranged from 0.46 to 0.52 for the 5 patients studied. Four of these values were 0.50 or 0.52, and for these patients (tables 1, 3, 4 and 5) the values decreased during recovery to 0.44 to 0.48. Values above 0.48 were not observed in this laboratory when the same technic was utilized on a group of normal subjects.

Excretion of Pigment.—The excretion of blood pigment in the stools and urine was measured for the purpose of ascertaining whether there was a relation to changes in the total red blood cell mass. There was marked variation in the quantity of urobilinogen excreted in the various four day periods; this was noted in respect to the individual patient as well as in regard to the entire group studied. The quantity of pigment excreted in the feces for all the periods of study varied from 19 to 305 mg. per day. For the patients of cases 2 and 4 the values for pigment excretion were seemingly related to the decrease in the total blood cell mass. The initial pigment excretion of 2 of the 5 patients was at or slightly above the maximum normal value (280 mg. per day) reported by Watson.[10]

The urinary excretion of pigment of 2 patients (tables 3 and 4) was abnormally increased during the first period following admission to the hospital and decreased coincident with clinical improvement.

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10. Watson, C. J.: Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937.

TABLE 3.—*Findings in Case 3 (J. G.).* Diagnoses: Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries and Congestive Heart Failure*

Days of Study	Weight, Kg.	Total Blood Volume,† Cc.	Plasma Volume,† Cc.	Red Cell Mass,† Cc.	Hematocrit,† Per Cent Cells	Reticulocytes, Average Per Cent	Serum Bilirubin, Mg. per 100 Cc.	Urine Volume, Average Cc. per Day	Urinary Pigment, Average Mg. per Day	Fecal Pigment, Average Mg. per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Clinical Findings
1- 4	96.5	8,500	4,150	4,350	53.2	2.7	1.8	1,242	14.0	282	0.52	Loss of ascites and sacral edema
5- 8	87.2	.....	.....	.....	....	2.0	...	742	2.5	71	....	Minimal ankle edema
9-12	86.4	7,900	3,720	4,180	54.1	0.9	1.3	380	2.1	119	0.54	Loss of cyanosis and rales
13-16	83.7	.....	.....	.....	....	0.5	...	1,751	1.5	39	....	
17-20	82.4	7,700	3,760	3,940	51.7	0.7	1.4	298	0.9	137	0.52	Reappearance of rales and cyanosis
21-24	82.0	.....	.....	.....	....	0.8	...	1,552	1.9	233	....	Persistent cyanosis, loss of rales
25-28	81.0	7,700	3,700	4,000	53.9	0.5	1.2	398	1.0	39	0.48	Reappearance of ankle edema
29-32	81.0	.....	.....	.....	....	0.6	...	920	0.8	70	....	
33-36	79.6	7,600	3,680	3,920	52.6	0.7	1.4	1,170	6.0	124	0.48	Loss of edema
37-40	76.4	.....	.....	.....	....	0.2	...	1,400	1.1	152	....	Discharged with cyanosis and orthopnea
41	75.0	7,230	3,520	3,710	51.5	...	...	.....	...	...	....	

* The patient was a 53 year old woman, 162 cm. in height. The normal calculated blood volume is 3,700 cc.
† These observations were made on the first day of each four day period.

Serum Bilirubin.—The serum bilirubin was elevated in 3 (tables 2, 3 and 4) of the 4 patients with peripheral evidences of congestive failure and decreased during the period of hospitalization.

COMMENT

An understanding of the metabolism of the blood is desirable in evaluating the changes, both clinical and physiologic, occurring in association with congestive heart failure. In the earliest stages of congestive failure, before the development of discernible edema and increased venous pressure, profound alterations in the circulatory dynamics are already present.[11] These include definite venous engorgement together with increase in the cross-sectional diameter of the flowing blood stream and consequent slowed velocity of blood flow. When patients enter the hospital with pronounced signs of congestive failure the blood volume is greatly increased, as shown by the data of this study and of those of others.[1] The level of the hematocrit under such circumstances is the result of the relative increase in plasma volume and red blood cell mass. The observed increase in the total red cell mass is to be related to active erythrocyte production, denoted by reticulocytosis.

During recovery from congestive failure, the blood volume decreases because of a reduction of the volume of both the plasma and the red cell mass; the reticulocyte percentage decreases. Before the first noticeable clinical improvement there is a preponderant reduction of the plasma volume [1c] as evidenced by the increase in the level of the hematocrit. This is followed by destruction of red cells and a further decrease in the total blood volume.

Pigment Excretion in the Stools.—The amounts of urobilinogen excreted in the feces in the cases of this study were analyzed in relation to changes in blood volume as observed by serial measurements. The urobilinogen studies were made in an attempt to discover whether the destruction of red cells as indicated by measurements of blood volume taken during recovery from congestive heart failure would be reflected by increased excretion of the blood pigment.

In the case of 2 patients (tables 2 and 3) during the first period of observation the excretion of urobilinogen in the stools was at or above the upper limit for normal ambulatory patients reported by Watson.[10] There was in general no quantitative relation between reduction in the total red cell mass and the excretion of pigment in the stools.[12]

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11. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: V. The Physiological and Pathological Significance of the Velocity of Blood Flow, J. Clin. Investigation **4**:199, 1927.

12. In studying normal ambulatory subjects Watson [10] found that the daily excretion of urobilinogen calculated from four day periods varied from 40 to 280 mg. and averaged 190 mg.

TABLE 4.—*Findings in Case 4 (W. W.).* Diagnoses: Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Heart Failure, Angina Pectoris, Mitral Insufficiency and Aortic Stenosis*

Days of Study	Weight, Kg.	Total Blood Volume,† Cc.	Plasma Volume,† Cc.	Red Cell Mass,† Cc.	Hematocrit,† Per Cent Cells	Reticulocytes, Average Per Cent	Serum Bilirubin, Mg. per 100 Cc.	Urine Volume, Average Cc. per Day	Urinary Pigment, Average Mg. per Day	Fecal Pigment, Average Mg. per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Vital Capacity, Cc.	Clinical Findings
1- 4	66.1	5,880	3,330	2,550	44.4	1.8	4.0	850	18.0	148	0.52	1,200	Extremis, anasarca, cyanosis
5- 8	63.6	.....	.....	.....	42.0	1.2	...	2,449	10.5	199	0.46	.....	
9-12	57.3	5,280	3,160	2,120	40.5	1.3	2.1	2,210	20.1	75	0.44	.....	Loss of edema and anasarca
13-16	....	.....	.....	.....	....	1.1	...	1,210	4.7	38	....	1,700	
17-20	48.6	4,560	2,540	2,023	44.0	0.0	1.5	1,047	3.0	40	0.44	.....	No orthopnea, cyanosis or rales
21-24	47.4	.....	.....	.....	....	0.0	...	927	2.8	27	....	2,500	No signs or symptoms of failure
25	46.8	4,620	2,672	1,948	41.2	...	1.6	.....	...	..	....	.....	

* The patient was a 59 year old man, 162 cm. in height. The normal calculated blood volume is 4,600 cc.
† These observations were made on the first day of each four day period.

TABLE 5.—*Findings in Case 5 (D. N.).* Diagnoses: Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Left Ventricular Failure and Angina Pectoris*

Days of Study	Weight, Kg.	Total Blood Volume,† Cc.	Plasma Volume,† Cc.	Red Cell Mass,† Cc.	Hematocrit,† Per Cent Cells	Serum Bilirubin, Mg. per 100 Cc.	Urine Volume, Average Cc. per Day	Urinary Pigment, Average Mm. per Day	Fecal Pigment, Average Mg. per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm. of Water	Clinical Findings
1- 4	62.2	3,525	2,155	1,370	39.6	0.3	815	0.2	54	0.50	90	Loss of cough and cyanosis
5- 8	62.2	.....	.....	.....	....	...	737	Trace	43	....	..	
9-12	61.3	4,070	2,624	1,446	36.8	0.3	440	Trace	88	0.48	85	Loss of rales and orthopnea
13-16	61.5	.....	.....	.....	....	...	345	Trace	24	....	..	Symptom free
17	61.0	3,740	2,400	1,340	34.6	0.2	...	...	..	0.48	85	

* The patient was a 59 year old woman, 151 cm. in height. The normal calculated blood volume is 3,500 cc.
† These observations were made on the first day of each four day period.

In five single periods of four days each in his observations of 5 patients with congestive failure, Watson [13] failed to find an increased urobilinogen excretion in the stools. Ehrstrom,[14] on the other hand, after using the method of Heilmeyer and Oetzel,[15] concluded that fecal urobilinogen is increased coincident with or shortly after the decrease in reticulocyte percentage during congestive failure. It should be noted, however, that Heilmeyer and Oetzel, in a study of 14 normal subjects, found that the daily fecal excretion of urobilinogen, calculated from eight to ten day periods, ranged from 70 mg. to 253 mg. Ehrstrom in observations on 1 normal subject found an average daily fecal output of 83 mg. of urobilinogen. The fecal urobilinogen output of the 8 patients with congestive failure studied by Ehrstrom was in all instances well within the normal limits defined by Heilmeyer and Oetzel. Weiss [16] also reported that the fecal output of urobilinogen associated with congestive failure in general shows a tendency to be increased, although the data show no distinct differences from the normal.

In general the results of our study, like the results of those already referred to, show during congestive failure no significant deviation from the normal values. The difficulties in interpreting the data are due to several causes. Variations in fecal urobilinogen output are great, making it more difficult to interpret values as abnormal unless they are clearly beyond the upper limits found in normal subjects. The normal values reported by Watson [10] were observed in studies of ambulatory patients, and it is entirely possible that lower values would be observed for normal subjects kept in bed, who would therefore be in a state more comparable to that of patients with congestive failure. Watson [10] found values ranging from 9 to 94 mg. for 5 patients with mild infection, inanition or inactivity and no jaundice or anemia. Whether similar findings would be observed for normal subjects at rest in bed, who would serve as more suitable normal controls for the patients in our series, cannot be stated on the basis of the evidence now available. That lower values might be obtained for such persons is suggested by the fact that the fecal excretion of pigment in our series tended to be low at the conclusion of the various periods of observation, when the peripheral evidences of con-

13. Watson, C. J.: Studies of Urobilinogen: III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, Arch. Int. Med. **59**:206 (Feb.) 1937.

14. Ehrstrom, M. C.: Blutstoffwechsel und Urobilinurie bei Herzinsuffizienz, Acta med. Scandinav. **88**:517, 1936.

15. Heilmeyer, L., and Oetzel, W.: Blutfarbstoffwechselstudien: II. Ergebnisse bei Gersunden, Diätversuche. Der Blutfarbstoffwechsel im Hunger, Deutsches Arch. f. klin. Med. **171**:365, 1931.

16. Weiss, M.: Ueber Urobilin und seine diagnostische Verwertung, Wien. Arch. f. inn. Med. **20**:38, 1930.

gestive failure had either disappeared or were less marked (tables 1, 2 and 4). Repeated determinations on the same subjects suggest that the variations for a given person are less than those observed in different periods. With the exceptions of the patient (case 3) in whom orthopnea and cyanosis were still present at the end of observation, the values for the last period of study were less than 60 mg. per day and averaged 41 mg. for those patients who had shown signs of congestive failure (cases 1, 2 and 4). Although these results suggest an increased output of urobilinogen during the height of congestive failure, conclusions cannot confidently be drawn, particularly since there was no definite correlation in some instances between decreases in total cell mass and periods of increased fecal excretion of urobilinogen. The problem is made the more difficult by the fact that it is not certain that in all conditions the breakdown of hemoglobin will be reflected in increased amounts of urobilinogen in the stools. In this connection it should be noted that in certain instances of paroxysmal nocturnal hemoglobinuria, obvious marked blood destruction has been attended by no or only slight increased urobilinogen (or porphyrin) excretion.[17]

Urinary Excretion of Urobilinogen.—The urinary excretion of urobilinogen of 2 of the patients studied (tables 3 and 4) was elevated in the presence of pronounced manifestations of congestive failure and diminished as clinical improvement occurred. The increased excretion of urobilinogen in the urine is evidently related to the decreased excretory function of the liver. In these 2 patients the liver was markedly enlarged. Similar observations have been reported by other investigators.[18] In the cases of congestive failure studied by these authors, urobilinuria likewise was not of constant occurrence. In the 11 cases studied by Watson [18] tenderness of the liver was regularly noted in those patients showing urobilinuria. Variations in urobilinuria were independent of the volume of urine excreted (tables 1 through 5).

Serum Bilirubin.—Increases of serum bilirubin similar to those observed by us in studying some patients with congestive failure have been described by others.[19] This elevated serum bilirubin is to be attributed to decreased function of the liver resulting from arterial anoxemia and congestion.[19] In the absence of pulmonary infarction [20]

17. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, Arch. Int. Med. **64**:1271 (Dec.) 1939.

18. (*a*) Jolliffe, N.: Liver Function in Congestive Heart Failure, J. Clin. Investigation **8**:419, 1930. (*b*) Watson.[18] (*c*) Weiss.[16]

19. Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937.

20. Keefer, C. S., and Resnick, W. H.: Jaundice Following Pulmonary Infarction in Patients with Myocardial Insufficiency: I. A Clinical Study, J. Clin. Investigation **2**:375, 1926.

the serum bilirubin rarely becomes sufficiently increased in persons with congestive failure to cause clinical jaundice.[19]

Fragility of the Red Blood Cells.—The fragility of the red blood cells was increased in the presence of congestive failure and was seemingly related to the degree of cyanosis clinically. With recovery, the minimum osmotic resistance of the red cells to hypotonic solutions of sodium chloride returned toward normal. Francescon[21] and Greenthal and O'Donnell[22] also noted this increased fragility of erythrocytes in association with congestive failure. The anoxemia and stasis of congestive failure are presumably responsible for the increased erythrocyte fragility, since complete arrest of the circulation of the arm in normal subjects by the blood pressure cuff likewise results in an increased fragility of the red blood cells. These studies are the subject of a separate communication by one of us.[23]

The finding of increased fragility in cases of congestive heart failure suggests that the anoxemia of this condition leads to an elevation of the serum bilirubin not only predominantly by its effect on liver function but also in part by causing an increased destruction of red blood cells.

Reticulocytosis.—The finding of reticulocytosis, with the percentage of reticulocytes ranging from 1.2 to 2.7, in the 4 patients with peripheral evidences of congestive failure denotes active blood production stimulated by anoxemia. The degree of reticulocytosis observed by us is similar to that observed by Ehrstrom.[14] In other patients we have observed a percentage of reticulocytes as high as 4.8. Impaired oxygenation in other conditions likewise causes reticulocytosis. Szour and Bergenbaum[24] reported such changes accompanying chronic pulmonary tuberculosis, and similar findings are present in association with adaptation to atmosphere of low oxygen tension.[25]

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21. Francescon, M.: Comportamento della resistenza osmotica die globuli rossi e del ricambio emoglobinico nei cardiopazienti in fase acuta di scompenso e in fase compensatoria, Minerva med. **37**:255, 1936.

22. Greenthal, R. M., and O'Donnell, W. S.: Studies on the Fragility of the Red Blood Cells, Am. J. Physiol. **58**:271, 1921.

23. Waller, J. V.: Cause of Increased Fragility of Erythrocytes in Congestive Heart Failure, Proc. Soc. Exper. Biol. & Med. **42**:64, 1939.

24. Szour, M., and Bergenbaum, C.: Retikulozytenuntersuchungen bei Lungentuberkulose, Wien. klin. Wchnschr. **47**:1583, 1934.

25. Barcroft, J.; Binger, C. A.; Bock, A. V.; Boggart, J. H.; Forbes, H. S.; Harrop, G.; Meakins, J. C., and Redfield, A. C.: Report to the Peru High-Altitude Committee: VIII. Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body, Carried Out in the Peruvian Andes, Chiefly Cerro de Pasco, Phil. Tr. Roy. Soc. London **211**:350, 1923.

SUMMARY AND CONCLUSIONS

We believe that in relating the data observed in our studies to each other and to the clinical manifestations of congestive heart failure, certain general conclusions can be stated. In the presence of pronounced manifestations of congestive heart failure with increased venous engorgement and elevated pressure, the plasma volume and total red cell mass are increased, the red cell fragility is increased and the reticulocyte percentage is elevated. The excretion of urobilinogen in the urine and the serum bilirubin concentration are frequently elevated, probably as a result of the impaired liver function resulting from anoxemia. As clinical recovery progresses and the total blood volume decreases, the loss in plasma tends at first to be somewhat greater than the decrease in total red cell mass, resulting in a slight temporary elevation of the hematocrit. The excretion of urobilinogen in the stools, although at no time significantly increased above the normal values for ambulatory patients, generally shows higher values during the periods of blood destruction than when the evidences of congestive failure become less marked. During the phase of contracting blood volume the reticulocyte percentage decreases, while the values for red cell fragility, serum bilirubin and urinary urobilinogen become normal.

COMPARISON OF SULFATHIAZOLE AND SULFAPYRIDINE IN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

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CLEVELAND

The comparative effectiveness and toxicity of sulfathiazole 2-sulfanilamidothiazole and sulfapyridine in the treatment of pneumococcic pneumonia has been reported by Flippin, Schwartz and Rose.[1] The corrected mortality for the sulfathiazole-treated series was 7.4 per cent and for the sulfapyridine-treated series 11.4 per cent. Sulfapyridine reduced the temperature more rapidly than sulfathiazole, but the average number of hospital days for patients in the two groups was the same, thirteen and two-tenths days. The severity and frequency of nausea and vomiting were less in the group of patients treated with sulfathiazole. Other toxic manifestations were approximately equally frequent.

At Cleveland City Hospital from January to June 1940, 40 patients with typed pneumococcic pneumonia were treated with sulfathiazole[2] and 62 with sulfapyridine. Eighteen extremely ill patients (5 in the sulfathiazole-treated group and 13 in the sulfapyridine-treated group) received specific antipneumococcus serum intravenously in addition to chemotherapy. One or more blood cultures, roentgen films of the chest, repeated blood counts, urinalyses and determinations of the free drug in the blood were made for every patient.

DOSAGE

Sulfathiazole.—The initial dose of sulfathiazole was 4 Gm. by mouth, repeated in four hours, followed by 2 Gm. every four hours until clinical improvement occurred. Then 1 Gm. was given every four hours until the temperature was normal for two to three days and clinical improvement was definite. The average total dose was 53.3 Gm. in five and

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1. Flippin, H. F.; Schwartz, L., and Rose, S. B.: The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, Ann. Int. Med. **13**:2038-2049 (May) 1940.

2. Sulfathiazole was available for study through cooperation with the Squibb Institute for Medical Research and the Medical Research Division of the Winthrop Chemical Co., Inc.

three-tenths days, or 10.1 Gm. per day. This dose produced an average level of 5.8 mg. of free sulfathiazole per hundred cubic centimeters of blood.

Sulfapyridine.—The initial dose of sulfapyridine was 2 Gm., followed by 1 Gm. every four hours for five doses and then 1 Gm. every six hours until the temperature was normal for two to three days and clinical improvement was established. The average total dose was 34.4 Gm. in six and eight-tenths days, or 5.1 Gm. per day. This dose produced an

TABLE 1.—*Distribution of Types, Bacteremia and Mortality*

	Sulfathiazole-Treated Group				Sulfapyridine-Treated Group			
	All Patients		Patients with Bacteremia		All Patients		Patients with Bacteremia	
Type	Number	Died	Number	Died	Number	Died	Number	Died
I	11	3	1	1	17	3	3	1
II	6	..	..	..	8	3	1	1
III	6	1	1	1	12	2	..	..
IV	2	..	..	..	3	1	..	..
V	2	..	..	..	2	..	1	..
VI	1	..	..	..	1	..	..	..
VII	4	..	..	..	4	..	..	..
VIII	4	..	1	..	4	..	1	..
IX	1	1	..	..	..	..	..	..
X	..	..	..	..	1	1	1	1
XI	..	..	..	..	1	1	..	..
XII	..	..	..	..	3	..	..	..
XIV	2	..	1	..	1	..	..	..
XVI	..	..	..	..	1	..	..	..
XVIII	..	..	..	..	2	..	..	..
XIX	1	..	..	..	1	..	..	..
XXIII	..	..	..	..	1	..	..	..
Total	40	5	4	2	62	11	7	3
Mortality per cent	12.5		50.0		17.7		42.8	
Corrected mortality per cent *	10.3		33.3		8.9		20.0	

* Seven patients (1 treated with sulfathiazole and 6 treated with sulfapyridine) who died within twenty-four hours after admission are excluded; 3 of these patients had bacteremia (1 treated with sulfathiazole and 2 treated with sulfapyridine).

average concentration of 5.4 mg. of free sulfapyridine per hundred cubic centimeters of blood. With both drugs about 3,000 cc. of fluid was given to each patient each day.

THERAPEUTIC RESULTS

The therapeutic results are tabulated in table 1. There were 5 deaths in the group treated with sulfathiazole (table 2) and 11 deaths in the group treated with sulfapyridine (table 3). Exclusive of the patients who were moribund on admission and died within twenty-four hours, the corrected mortality is 10.3 per cent for the sulfathiazole-treated group and 8.9 per cent for the sulfapyridine-treated group.

The average age of the patients treated with sulfathiazole was 38.1 years and that of the patients treated with sulfapyridine 44.8. Treatment was begun on the third and six-tenths day of the disease in the

TABLE 2.—*Analysis of Causes of Death in the Sulfathiazole-Treated Group* *

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	Number of Lobes Involved	Total Dose of Drug, Gm.	Amount of Total Serum, Units	Comment
1	41	22	IX	Negative	2	25	—	Rheumatic heart disease; mitral stenosis; cardiac failure; no response to treatment; no autopsy
2	68	2	I	Negative	4	72	—	No response to treatment; autopsy: lobar pneumonia of right lung showing organization and resolution, bronchopneumonia in left lung, abscesses in right lung; hepar lobatum
3	58	8	I	Positive	1	68	200,000	Response to treatment for 7 days; relapse and death on 14th hospital day; no autopsy
4	54	3	I	Negative	3	86	—	Temporary response to treatment, relapsed; autopsy: lobar pneumonia in right lung, abscess of upper lobe of right lung, chronic pyelonephritis, heart weight 500 Gm.
5	46	2	III	Positive	3	6	—	Moribund on admission: death in 10 hours; no autopsy

* The autopsies were performed by members of the staff of the department of pathology of Cleveland City Hospital; division chief, Dr. H. T. Karsner.

TABLE 3.—*Analysis of Deaths in the Sulfapyridine-Treated Group* *

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	Number of Lobes Involved	Total Dose of Drug, Gm.	Amount of Total Serum, Units	Comment
1	70	2	I	Negative	2	43	300,000	No response to treatment; no autopsy
2	76	3	I	Negative	2	22	—	No response to treatment; no autopsy
3	63	3	IV	Negative	2	27	200,000	Chronic alcoholism, pellagra; no response to treatment; autopsy: bilateral confluent bronchopneumonia
4	77	?	XI	Negative	2	28	—	Hypertensive heart disease with auricular fibrillation and cardiac failure; no response to treatment; no autopsy
5	50	14	I	Positive	2	50	—	No response to treatment; autopsy: bilateral organizing bronchopneumonia with abscess formation, acute vegetative endocarditis of tricuspid valve
6	53	6	II	Positive	2	4 (vomiting at once)	—	Moribund on admission; death in 3½ hours; no autopsy
7	41	7	X	Positive	2	15	—	Moribund on admission: rheumatic heart disease with severe cardiac failure; death in 15 hours; autopsy: rheumatic heart disease, heart weight 710 Gm., bilateral bronchopneumonia
8	58	3	III	Negative	2	3	—	Moribund on admission; death in 11 hours; no autopsy
9	37	9	II	Negative	4	12	—	Moribund on admission; death in 16 hours; autopsy: lobar pneumonia in 4 lobes
10	84	21	III	Negative	3	4	—	Moribund on admission; death in 20 hours; autopsy: lobar pneumonia in 3 lobes, rheumatic heart disease, severe coronary arteriosclerosis
11	61	5	II	Negative	3	10	—	Moribund on admission; death in 18 hours; no autopsy

* The autopsies were performed by members of the staff of the department of pathology of Cleveland City Hospital; division chief, Dr. H. T. Karsner.

sulfathiazole-treated group and on the fourth and four-tenths day in the sulfapyridine-treated group. An average of 1.6 lobes was involved in the patients receiving sulfathiazole and of 1.5 lobes in those receiving sulfapyridine. There was no statistically significant [3] difference between the two groups as to sex and color.

EFFECT OF TREATMENT ON COURSE OF THE DISEASE

Exclusive of patients who died, there was a critical fall in temperature within twenty-four hours in 45.7 per cent of the sulfathiazole-treated group, as compared with 54.9 per cent of the sulfapyridine-treated group. At the end of forty-eight hours an additional 8.6 per cent of the sulfathiazole-treated group had had a critical fall in temperature, as compared with an additional 13.7 per cent of the other group. In the former group, 14.3 per cent had a normal temperature within twenty-four hours, an additional 14.3 per cent within forty-eight hours and an additional 20.0 per cent within seventy-two hours. In the latter group, 13.7 per cent had a normal temperature within twenty-four hours, an additional 33.3 per cent within forty-eight hours and an additional 5.9 per cent within seventy-two hours. After the temperature had once reached normal, a secondary rise above 37.5 C. (99.5 F.) occurred in 71.4 per cent of the patients treated with sulfathiazole, as compared with 78.4 per cent of those who received sulfapyridine. In the majority of instances this was of no consequence. The average number of hospital days for patients in each group was identical, seventeen and four-tenths days.[4]

COMPLICATIONS

In the group treated with sulfathiazole, pleural effusion occurred in 2 patients (slight in 1), empyema in 1, slow resolution in 1 and pulmonary abscess in 2. In the group treated with sulfapyridine, empyema occurred in 4 patients, slow resolution in 1 and pulmonary abscess in 2.

TOXIC REACTIONS

Nausea and vomiting were the most frequent toxic reactions. One third of the patients receiving sulfathiazole experienced vomiting, but it was almost uniformly mild. Approximately one half of the patients treated with sulfapyridine vomited, and the vomiting was more severe.

3. In this article the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

4. This does not include patients who died or who remained in the hospital for further study or treatment of accompanying conditions.

Crystals of the drug were found in the urine of 61.5 per cent of the patients receiving sulfathiazole and in 28.6 per cent of those receiving sulfapyridine. This difference is statistically highly significant. The incidence of microscopic hematuria was 18 per cent for sulfathiazole and 10.7 per cent for sulfapyridine. One patient receiving sulfathiazole had retention of nitrogenous products and oliguria for thirty-six hours, and another had renal colic (the renal disturbance was presumably due to crystals of the drug in both instances). The incidence of dermatitis was 7.7 per cent for sulfathiazole and 5.4 per cent for sulfapyridine. Granulocytopenia due to sulfathiazole was suspected in 1 instance, but the diagnosis was not established.

COMMENT

The experience of Cleveland City Hospital indicates that in the treatment of pneumococcic pneumonia approximately twice as much sulfathiazole as sulfapyridine is required to maintain an average concentration of 5 to 6 mg. of the free drug per hundred cubic centimeters of blood. In accordance with Flippin, Schwartz and Rose,[1] no significant difference in mortality between treatments with the two drugs was found. In the Cleveland series the patients treated with sulfapyridine were probably sicker, since they were 6.7 years older and had had their disease eight-tenths of a day longer. This is partially counteracted by the fact that the patients treated with sulfapyridine showed an average of one tenth of a lobe less involvement and that more serum was used in this group.

In both the Philadelphia[1] and the Cleveland series, sulfapyridine was found to bring the temperature down more rapidly. When the figures from the two sources are combined it is found that of 123 patients treated with sulfathiazole, 60 (48.8 per cent) had a critical fall in temperature in twenty-four hours, whereas of 136 patients treated with sulfapyridine, 84 (61.8 per cent) had a critical fall in temperature in twenty-four hours. This difference is statistically significant. Likewise, of 123 patients treated with sulfathiazole, 50 (40.6 per cent) had a normal temperature in forty-eight hours, whereas of 136 patients treated with sulfapyridine, 84 (61.8 per cent) had a normal temperature in forty-eight hours. This difference is highly significant statistically. Of the 123 patients in the sulfathiazole-treated group, 31 (25.2 per cent) had a secondary rise in temperature, in contrast to 52 (38.2 per cent) of the 136 patients in the sulfapyridine-treated group. This difference is statistically significant. In both series the number of hospital days was the same for both groups.

Again, combination of the figures from both sources shows that vomiting is markedly less frequent during treatment with sulfathiazole; in

fact, the difference is statistically highly significant. Sulfathiazole caused crystals in the urine more often in the Cleveland series. Otherwise the incidence of toxic reactions was not significantly different.

SUMMARY

From January to June 1940, inclusive, 40 patients with typed pneumococcic pneumonia were treated with sulfathiazole and 62 patients with sulfapyridine. It was found that approximately twice as much sulfathiazole as sulfapyridine was required to maintain an average concentration of 5 to 6 mg. of free drug per hundred cubic centimeters of blood. No significant difference in mortality between the two groups was demonstrated, the corrected mortality for the sulfathiazole group being 10.3 per cent and for sulfapyridine 8.9 per cent. Sulfapyridine brought the temperature down to normal more rapidly, but a secondary rise was more common. The length of stay in the hospital was the same in both groups. Sulfathiazole caused less vomiting but more crystals in the urine. Otherwise toxic manifestations were not significantly different.

ACACIA IN THE TREATMENT OF THE NEPHROTIC SYNDROME

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The use of acacia intravenously in the treatment of nephrotic edema was first employed in a systematic manner by Hartmann and his associates [1] in 1933. They reported careful observations on 6 patients, all children, 5 of whom showed a satisfactory diuretic response after acacia was used (table 1). The daily dose amounted to 1 to 2 Gm. per kilogram of body weight in the majority of the cases. If necessary, administration was repeated at intervals of one day, two days or more. Of special interest is the observation of these authors that the renal lesion is likely to improve as diuresis is established, as was shown in their cases by a diminished amount of casts and a lessened degree of albuminuria. Improvement in renal function in 1 case was so great that a normal condition was completely reestablished, as was shown by absence of edema, normal urinary findings and a normal content of protein in the serum.

The reason for administration of acacia is obvious. The colloid osmotic pressure of the serum in cases of nephrotic edema is subnormal, and intravenous administration of a colloidal solution of acacia, of which a 6 per cent solution in physiologic solution of sodium chloride has a colloid osmotic pressure considerably higher than that of the serum of a patient with nephrotic edema, could be very helpful in restoring, at least in part, the deficient colloid osmotic pressure of the serum of the recipient. Thus, according to the generally accepted hypothesis of the pathologic physiology underlying the nephrotic type of edema, the water which is stored in the tissues in excess can be mobilized more readily and can be excreted with the urine.

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* At the time this work was done, Dr. Goudsmit was a Fellow in Medicine of the Mayo Foundation.

1. Hartmann, A. F.; Senn, M. J. E.; Nelson, M., and Perley, A.: The Use of Acacia in the Treatment of Edema, J. A. M. A. **100**:251-254 (Jan. 28) 1933.

Encouraged by the results obtained by Hartmann and his co-workers, Austin and McGuinness [2] decided to treat in similar fashion an adult patient who had acute nephritis in which nephrotic elements were outstanding. After administration of 120 Gm. of acacia in 800 cc. of hypertonic saline solution, a very serious syndrome developed which necessitated venesection for its relief; apparently this was due to a sudden and excessive increase in the volume of the circulating blood. However, almost simultaneously the edema started to become mobilized, and soon it had completely disappeared. Thus, in their report, while they substantiated the desirable diuretic effects which can be obtained through the use of acacia, the authors warned against the injection of large quantities of this substance within too brief a period.

TABLE 1.—*Results of Treatment for Nephrotic Edema with Acacia Reported in the Literature*

Authors	Patients	Hospital Admissions	Results	
			Free or Nearly Free of Edema	Failures
Hartmann and others,[1] 1933	6	6	5	1
Austin and McGuinness,[2] 1933	1	1	1	..
Dick, Warweg and Andersch,[3] 1935	4	4	..	4
Barach and Boyd,[4] 1935	2	2	2	..
Boone,[5] 1937	1	1	1	..
Lepore,[6] 1937	4	5	5	..
Kerkhof,[8] 1937	1	1	1	..
Landis,[9] 1937	6	6	6	..
Shelburne,[10] 1938	3	3	3	..
Total	28	29	24	5

The experiences of Dick, Warweg and Andersch [3] were much less favorable than those of Hartmann and his co-workers and of Austin and McGuinness. Hardly any improvement in the clinical condition of 4 children who had nephrotic edema could be attributed to the use of acacia. In their paper special attention was given the fact that the concentration of proteins, already considerably less than normal prior to treatment, usually underwent further decrease subsequent to administration of a solution of acacia. The therapy thus more or less defeated its own purpose. In addition, the authors noted a considerable degree of swelling of the liver after administration of the colloidal solution of acacia, and they stated that this should be an additional reason for

2. Austin, J. H., and McGuinness, A. C.: Precaution Concerning the Treatment of Edema by Intravenous Administration of Acacia, Tr. A. Am. Physicians **48**:276-282, 1933.

3. Dick, M. W.; Warweg, E., and Andersch, M.: Acacia in the Treatment of Nephrosis, J. A. M. A. **105**:654-657 (Aug. 31) 1935.

caution in its use. It should be noted, however, that relatively large amounts of acacia were used by these authors. Thus, a girl 3 years of age received 285 Gm. in four months; another girl, 2 years of age, 129 Gm. in five weeks; a boy 6 years of age, 705 Gm. in six and a half months, and a boy 10 years of age, 492 Gm. in two and a half months.

Two cases of nephrotic edema in which acacia was used with considerable symptomatic improvement were reported by Barach and Boyd.[4] Their second patient, a boy 4 years of age, experienced diuresis after one dose of 21 Gm. of acacia, although all other treatment in the hospital during a period of seven months had been without effect. From that time on, the patient made a slow but satisfactory recovery.

Boone [5] noted that a 17 year old boy who had nephrotic edema lost 22 pounds (10 Kg.) after administration of acacia. A second course of acacia combined with a single injection of salyrgan (mersalyl) decreased the weight of the patient another 19.8 pounds (9 Kg.). The loss took place at a rate of approximately 1½ pounds (0.7 Kg.) a day, and the patient was dismissed with only a small amount of residual edema.

Four cases of nephrotic edema were studied by Lepore.[6] In all of these a satisfactory response to acacia was obtained; the patients became nearly free of edema soon after acacia was administered. The author observed considerable increase in the volume of circulating plasma after injection of acacia, and in his opinion, which is fortified by a statement of Peters,[7] this in turn was responsible for the diuretic response.

Kerkhof,[8] in his study of colloid osmotic pressure of plasma as a factor in the formation of edema, reported 1 case of subacute glomerulonephritis with edema in which treatment with acacia gave gratifying results. Within three days 300 Gm. was administered, raising the colloid osmotic pressure of the serum from 8 mm. to 15 mm. of mercury.

Landis [9] also has observed copious diuresis in 6 cases of nephrotic edema after administration of acacia. In 1 of his cases the diuretic response did not occur until after administration of aminophylline (theophylline with ethylenediamine). However, prior to administration

4. Barach, J. H., and Boyd, D. M.: Hypoproteinemic Nephrosis and Its Treatment with Acacia: Report of Two "Cured" Cases, Am. J. M. Sc. **189**:536-544 (April) 1935.

5. Boone, J. A.: Gum Acacia in the Treatment of Nephritic Edema, New England J. Med. **216**:289-292 (Feb. 18) 1937.

6. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, Ann. Int. Med. **11**: 285-296 (Aug.) 1937.

7. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

8. Kerkhof, A. C.: Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, Ann. Int. Med. **11**:867-880 (Dec.) 1937.

9. Landis, E. M.: Observations on Acacia Therapy in Nephrosis, J. A. M. A. **109**:2030-2034 (Dec. 18) 1937.

of acacia the same drug had failed to produce diuresis, and in this connection the author suggested the possibility of a synergistic action between acacia and "ordinary" diuretics.

Three additional cases of nephrotic edema in which highly satisfactory results were obtained with the use of acacia have been reported by Shelburne.[10] The author stressed the point that acacia should be employed as a temporary agent to free the patient of edema while high protein diets are given to maintain the clinical improvement. Fishberg[11] stated that he obtained excellent diuresis in several cases by injection of acacia, "but in others, it failed."

Largely on the basis of the evidence submitted by Dick and his associates, McCann,[12] after reviewing (in 1936) the recent literature on Bright's disease, concluded that in view of such experiences "further use of acacia seems to be unwarranted." It would appear that this conclusion adequately depicts the contemporary opinion of many physicians who are treating patients with a nephrotic type of edema. Our experiences, gained especially during the last two years, in which rather extensive use of acacia was made, have been more favorable. Undesirable effects have been limited and have been relatively innocuous. At the same time, the incorporation of acacia in the regimen of treatment for the nephrotic syndrome has resulted in an effective and efficient reduction of edema in the vast majority of cases. A summary of our clinical experiences thus appears in order.

GENERAL CONSIDERATIONS

Early Experiences with Acacia.—Prior to 1937 at the Mayo Clinic acacia had been used in only a few cases of nephrotic edema. One of us (M. W. B.),[13] in 1936, stated that the results, although sometimes encouraging, had not been as good as those obtained by Hartmann and his associates but indicated that this might be due to lack of experience. Our particular interest in acacia as a therapeutic agent in the nephrotic type of edema was aroused in the spring of 1937, when a patient whose edema was resistant to many forms of diuretic therapy which are usually successful was treated with acacia. The case has been reported in detail

10. Shelburne, S. A.: Rational Use of Acacia in Treatment of the Nephrotic Syndrome, J. A. M. A. **110**:1173-1176 (April 9) 1938.

11. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939.

12. McCann, W. S.: Bright's Disease: A Review of Recent Literature, Arch. Int. Med. **57**:630-642 (March) 1936.

13. Binger, M. W., in discussion on Hartmann, A. F., and Perley, A. M.: Acacia in the Treatment of Nephrotic Edema, J. A. M. A. **106**:416 (Feb. 1) 1936.

elsewhere, but a summary of the essential points is presented in the following paragraphs because of its unusual interest.

A married woman aged 27 noticed an increase in weight eight weeks before registration at the clinic, followed somewhat later by swelling of the legs, decrease in the output of urine, increase in the size of the abdomen and swelling of such parts of the body as were dependent for more than a brief period. Physical examination gave essentially negative results except for a moderate amount of ascites and rather extensive edema of the lower part of the back, the labia and the legs. The volume of urine in the first twenty-four hours was 150 cc.; the specific gravity was 1.043. The urine[14] contained albumin grade 4 (on the basis of 1 to 4) and a few casts, but no erythrocytes. At the time of registration the concentration of urea in the blood was 42 mg.; that of cholesterol 833 mg., and that of serum protein 4.4 Gm., per hundred cubic centimeters. The albumin-globulin ratio was 1:5. A diagnosis of chronic glomerulonephritis with marked nephrotic features was made.

Fluids were limited, and a salt-free, high protein diet was prescribed (chart 1). Potassium nitrate, ammonium nitrate, aminophylline, salyrgan and thyroid, in addition to sodium bicarbonate, sucrose and dextrose given intravenously and an abdominal paracentesis, all were ineffective in reducing edema. On the eleventh day of hospitalization, 350 cc. of a 6 per cent solution of acacia was injected intravenously. Satisfactory diuresis ensued, and the patient's weight decreased. A second injection, of 500 cc. of a 6 per cent solution of acacia, the next day resulted in further diuresis and loss of weight. One day later, 2 cc. of salyrgan produced an extremely satisfactory output of urine. A few days later, the patient was dismissed from the hospital entirely free of edema. During the six days following the first injection of acacia, the patient lost 23.5 pounds (10.7 Kg.). The colloid osmotic pressure of the serum one day before dismissal was 79 mm. of water.

Particularly striking in this case was the fact that diuretics, especially salyrgan, which had been completely ineffective on three occasions during the first part of the period of hospitalization, displayed all of their customary diuretic action after administration of acacia.

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14. Urinalysis, blood urea determinations according to Van Slyke and Cullen and determinations of the blood urea clearance, concentration of cholesterol of the blood, concentration of the serum proteins and the albumin-globulin ratio were carried out according to the directions of J. C. Todd and A. H. Sanford (Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology, ed. 9, Philadelphia, W. B. Saunders Company, 1939). The colloid osmotic pressure of the serum was determined according to Butt and Keys, as described by Butt, Power and Keys: "The concentration of acacia in the serum, its rate of excretion and its effect on the colloid osmotic pressure following intravenous injection in cases of cirrhosis of the liver." The article (Butt, H. R.; Power, M. H., and Keys, A.: The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, J. Lab. & Clin. Med. **24**:690-695 [April] 1939) also describes Power's method for determining the concentration of acacia in serum, which was employed in the present study.

Diagnostic Criteria.—Since June 1937, 51 patients more than 14 years of age have received treatment for nephrotic edema at the Mayo Clinic. All had albuminuria grade 4, with or without casts or erythrocytes in the urinary sediment, an appreciably diminished content of protein in the serum, a lowered or inverted albumin-globulin ratio and diminished colloid osmotic pressure of the serum. In the large majority of the cases there were increased values for cholesterol in the blood.

The diagnosis in all these cases was subacute or chronic glomerulonephritis of the nephrotic type, with or without renal insufficiency. We

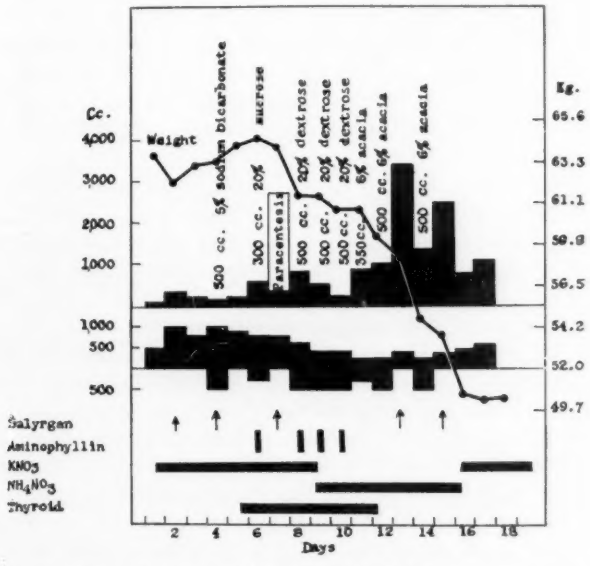

Chart 1 (case 1).—Essential factors of fluid balance in the case of a patient who had an unusually resistant type of nephrotic edema. Upper black blocks: volume of urine in each twenty-four hours. Lower black blocks: intake of fluid in each twenty-four hours (above zero line, oral intake; below zero line, intravenous intake); weight line as indicated. Medication: salyrgan (large arrow represents 2 cc. given intravenously; small arrow, 1 cc.); aminophylline, 4 grains (0.26 Gm.) in 10 cc. mixed with other solutions given intravenously; potassium nitrate and ammonium nitrate, 9 Gm. orally, daily, and desiccated thyroid gland, 9 grains (0.6 Gm. orally, daily). Reprinted from Goudsmit, A., and Binger, M. W.: Nephrotic Type of Edema Unusually Resistant to Treatment: Report of Case, Proc. Staff Meet., Mayo Clin. **12**:401-405 (June 30) 1937.

have refrained from using the diagnosis of "lipoid nephrosis" or "chronic nephrosis," since it appears that, although such a syndrome may exist entirely apart from chronic glomerulonephritis, one can never predict

whether sooner or later there will develop signs or symptoms such as erythrocytes in the urinary sediment, renal insufficiency or hypertension, which do not belong in the unadulterated picture of true lipoid nephrosis.

General Regimen.—All patients hospitalized for treatment of the nephrotic syndrome were given the standard salt-free [15] diet with 75 to 100 Gm. of protein per day. Various vitamins in the form of the pure crystalline compounds and concentrates were added to the diet in many instances. Fluids taken by mouth were limited to approximately 1,000 cc. daily, or less if the patient was able to tolerate the restriction. Potassium or ammonium salts in the form of nitrates or chlorides regularly supplemented the regimen. Of these salts, in view of the experiences of Keith and Binger,[16] potassium nitrate is preferred in the great majority of instances. It is given in the form of enteric coated pills of 0.5 Gm. each. Six to 12 Gm. per day is given with or after meals in doses of 2 to 4 Gm. each. The most commonly employed dose was 9 Gm. daily.

Necessity of Treatment for Edema.—The appearance of a nephrotic type of edema in a case of chronic glomerulonephritis is a serious complication. The accumulation of fluid should be treated promptly and thoroughly for many reasons. 1. The presence of edema lessens resistance to infection. 2. If the edema is not treated, gastrointestinal disorders and anorexia develop, resulting in malnutrition. 3. It is common experience that, as a group, patients who have chronic glomerulonephritis without edema have a much better prognosis than those with equally efficient renal function (as determined by the level of urea in the blood or by urea clearance tests) but with the condition complicated by massive edema. The excessive amount of water present in the tissue spaces probably impairs proper functioning of all vital organs but may well be especially harmful to organs already the site of disease. 4. Patients who have progressive edema soon become unable to carry on their usual activities. 5. The presence and persistence of edema produce anxiety and are a great strain on the patient's mental stability.

Patients Treated Without Acacia.—Of the 51 patients with nephrotic edema to whom treatment was given in the last two years, 14 became free of edema without the use of acacia (table 2). The success obtained in this group is tempered by the knowledge that if the patients had not

15. Of course the "freedom" from salt is only relative. Special bread and butter to which no extra salt is added during the processing must be employed. Milk, because of its rather high salt content, should be restricted. Thus, a so-called salt-free diet, served to contain approximately 2,000 calories per twenty-four hours, contains between 1 and 2 Gm. of sodium chloride.

16. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J. A. M. A. **105**:1584-1591 (Nov. 16) 1935.

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Patients Treated with Acacia.—Thirty-seven patients who had an uncomplicated nephrotic type of edema, 3 patients who had edema of mixed origin (partly nephrotic and partly nonnephrotic), 1 patient who

TABLE 2.—*Results of Treatment of Sixty-One Consecutive Hospitalized Patients* with the Nephrotic Syndrome at the Mayo Clinic Between July 1, 1937, and July 20, 1939*

Clinical Condition	Treatment	Cases	Hospital Admissions	Results †		
				Free of Edema	Nearly Free of Edema	Failures
Nephrotic syndrome with edema	Diet alone	3	3	3	..	..
	Diet and salyrgan	1	1	1	..	..
	Diet and KNO_3	10	10	10	..	..
	Included acacia	37	47	25	13	9
Nephrotic syndrome with edema part of which was nonnephrotic in origin §	Included acacia	3	3	2	1	..
Edema of acute exacerbation of chronic nephritis; associated exfoliative dermatitis	Included acacia	1	1	..	1	..
Nephrotic syndrome without manifest edema	"Prophylactic" use of acacia	10	10	..	..	..

* This number does not include 16 children up to 15 years of age who had the nephrotic syndrome and were seen during the same period.
† In relation to number of hospital admissions.
§ Histories of these 3 patients are presented in the text.

TABLE 3.—*Distribution of Patients According to Age and Sex*

Age, Years	Women		Men	
	Number	Per Cent	Number	Per Cent
15 to 24	5	33	7	28
25 to 34	7	47	4	16
35 to 44	..	..	5	20
45 to 54	2	13	4	16
55 to 64	1	7	3	12
65 to 74	..	..	2	8
Totals	15	100	25	100

had chronic nephritis and 10 patients who had the nephrotic syndrome without edema were treated with acacia (table 2). The distribution of these two groups according to age and sex is presented in table 3. The preponderance of men over women is evident and is worthy of note, since it is generally thought that women outnumber men in this regard. However, 80 per cent of the women were less than 35 years of age, whereas only 44 per cent of the men were under 35. Thus, it appears that inclusion of a comparatively large number of older men materially

whether sooner or later there will develop signs or symptoms such as erythrocytes in the urinary sediment, renal insufficiency or hypertension, which do not belong in the unadulterated picture of true lipoid nephrosis.

General Regimen.—All patients hospitalized for treatment of the nephrotic syndrome were given the standard salt-free [15] diet with 75 to 100 Gm. of protein per day. Various vitamins in the form of the pure crystalline compounds and concentrates were added to the diet in many instances. Fluids taken by mouth were limited to approximately 1,000 cc. daily, or less if the patient was able to tolerate the restriction. Potassium or ammonium salts in the form of nitrates or chlorides regularly supplemented the regimen. Of these salts, in view of the experiences of Keith and Binger,[16] potassium nitrate is preferred in the great majority of instances. It is given in the form of enteric coated pills of 0.5 Gm. each. Six to 12 Gm. per day is given with or after meals in doses of 2 to 4 Gm. each. The most commonly employed dose was 9 Gm. daily.

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affects the general distribution. We are not prepared to say whether this truly represents a high incidence in the population at large or whether the high proportion of men in the present series was conditioned by special sociologic factors.

Renal Insufficiency.—The incidence of renal insufficiency in the group receiving acacia was studied. Values for blood urea of 46 mg. per hundred cubic centimeters or less were considered as indicative of fundamentally sufficient renal function; thus, only patients in whose cases the values for blood urea were consistently higher than this figure have been considered as having renal insufficiency (this criterion was proposed by one of us [Goudsmit] and Keith [17]). From the data available it appears that renal insufficiency of itself does not necessarily influence the outcome of diuretic treatment. Thus, of 33 patients with uncomplicated nephrotic edema successfully treated with acacia, renal insufficiency was noted in 13. Of 7 patients in whose cases satisfactory diuresis was not obtained with acacia, 3 had renal insufficiency.

TECHNIC, REACTIONS AND RESULTS

In the last few months we have employed a 6 per cent solution of acacia in 0.06 per cent sodium chloride. Before that time most of the acacia was prepared in our own laboratory for intravenous solutions.

Preparation of Solution of Acacia.—Acacia in the form of lumps (pearls), no. 1, extra quality, is used. First, a solution of twofold strength (12 per cent) is prepared; this is then diluted to the required degree of concentration (6 per cent) with freshly triple-distilled water. Eight liters of this solution is prepared in the following manner: Weigh and place in a 4 liter beaker 480 Gm. of crushed acacia. Add to this 500 cc. of hot triple-distilled water, and stir with a glass rod. The acacia is extracted more readily if a small amount of hot water is added at a time. A large portion of the acacia dissolves rapidly. Carefully pour off from the residual material into a 12 liter round-bottomed pyrex flask the thick supernatant solution thus obtained. The residual material in the beaker is then reextracted of its acacia by adding another 500 cc. of hot water and by stirring and pouring off the supernatant solution thus obtained. This process of extraction is repeated until all of the material is dissolved. To this solution is added 72 Gm. of chemically pure sodium chloride,[18] and the total volume contained in a 12 liter

17. Goudsmit, A., Jr., and Keith, N. M.: Relative Significance of Concentration of Inorganic Sulfate in the Serum and of Its Renal Clearance, with Special Reference to Diffuse Arteriolar Disease with Hypertension, Arch. Int. Med. **66**:816 (Oct.) 1940.

18. If a final concentration other than 0.9 per cent sodium chloride is desired a different amount must be added.

pyrex flask is then increased to 8 liters. This turbid solution is autoclaved at a pressure of 18 pounds (8.2 Kg.) for periods of one hour on three consecutive days. This procedure results in the precipitation of some flocculent material. The solution, therefore, is thus filtered through a double layer of ordinary filter paper placed on top of a layer of cotton, which in turn rests on the funnel. The filtrate is reautoclaved a last time for one hour and then, under sterile conditions, is poured into sterile bottles.

Administration.—The acacia was usually administered as a 6 per cent solution. At first a preparation in 0.9 per cent sodium chloride was used; later, in view of the desirability of limiting the intake of sodium chloride, acacia in distilled water was employed. Also, concentrations of sodium chloride of 0.06 per cent and 0.15 per cent were used. Therapeutically we have not been able to detect any differences in the results obtained by use of these various solutions. In most instances, 500 cc. of a 6 per cent solution of acacia was given in one day, and forty-five

TABLE 4.—*Reactions Noted in the Course of One Hundred and Thirty Intravenous Injections of Solution of Acacia in Thirty-Three Patients with Successfully Treated Nephrotic Edema*

Reaction	Number	Per Cent
Urticaria	13	10
Thoracic discomfort	2	2
Fever (with or without chill)	5	4

to seventy-five minutes was allowed for its administration. It was given every day or on alternate days, as it seemed best tolerated.

Dosage.—The amount of acacia given in 41 instances in which it was successfully used in cases of nephrotic edema may be summarized as follows: In 17 cases, 90 Gm. was given, and in 11 cases, 120 Gm. Only once was as much as 150 Gm. and 156 Gm., respectively, given during one course of treatment, and in the remaining 11 cases the dose varied between 60 and 120 Gm. On completion of a course of acacia, the concentration of this substance in the serum was usually found to range between 1,000 and 2,500 mg. per hundred cubic centimeters.

Undesirable Effects.—A review of experience with 130 injections of acacia (table 4), comprising all cases of uncomplicated nephrotic edema treated successfully, reveals three different undesirable reactions which have occurred: (1) urticaria, (2) thoracic discomfort and (3) fever. Reactions of the urticarial type sometimes have been limited to the arm into which the injection was made but have occurred anywhere on the body shortly after the beginning of the injection or even a few hours after its completion. Subjective sensations of heat or flushing, in addition to

itching, sometimes accompanied the eruption. Usually the subcutaneous administration of 5 to 8 minims of epinephrine hydrochloride (1:1,000) will cope successfully with these symptoms, which in our experience have never lasted longer than twelve hours even without special medication.

Reactions in the form of thoracic discomfort are entirely subjective. They consist of substernal pain, dyspnea and sometimes sharp pain in the thorax, usually on the left side; sometimes there are diffuse thoracic pain and backache. This type of reaction is not accompanied by any changes in temperature, pulse or blood pressure, and nothing abnormal can be discovered on physical examination of the thorax. Subcutaneous injection of ½ to 1 grain (0.032 to 0.065 Gm.) of codeine sulfate usually is sufficient to alleviate the symptoms, but they may persist to some degree for as long as eighteen hours.

Fever, when it occurs, does not differ essentially from the fever that sometimes develops after a blood transfusion. Sometimes fever is initiated by a chill. On one occasion the fever lasted for two days; although we suspect that an intercurrent infection of the respiratory tract played some part in the causation of this fever, it has been included in our tabulation of disagreeable reactions to acacia.

Frequently a patient who had had a reaction to acacia on one occasion would go without any untoward sign or symptom after a subsequent injection. Conversely, reactions have become apparent only with the second or third injection. Maytum and Magath,[19] who reviewed experiences with 3,000 injections of a preparation of acacia similar to the one employed in the present series, mentioned only the development of hypersensitiveness as a hazard arising from its administration. We are confident that disagreeable reactions should be limited to the types noted by Maytum and Magath and by us, and we are convinced that the more serious reactions noted in the literature[20] must be due to inferior quality or improper preparation of the acacia.

Influence on Renal Function and on Blood Pressure.—It is our experience that intravenous administration of solutions of acacia does not influence unfavorably an underlying glomerulonephritic type of lesion. Neither does its administration cause an increase in blood pressure for longer than a day. We have seen actual improvements in renal function subsequent to its use, as judged by the concentration of urea in the blood and by results from urea clearance tests. Also,

19. Maytum, C. K., and Magath, T. B.: Sensitivity to Acacia, Proc. Staff Meet., Mayo Clin. **7**:216-217 (April 13) 1932; Sensitivity to Acacia, J. A. M. A. **99**:2251-2252 (Dec. 31) 1932.

20. Studdiford, W. E.: Severe and Fatal Reactions Following the Intravenous Use of Gum Acacia Glucose Infusions, Surg., Gynec. & Obst. **64**:772-784 (April) 1937.

secondary diffuse arteriolar disease with hypertension has become quiescent after treatment with acacia, as judged by return of the blood pressure to within normal limits and by disappearance of signs of active vasospastic retinitis.

Additional Diuretic Measures.—It is of interest to note (table 5) that more than half of the patients treated with restriction of diet, diuretic salts

TABLE 5.—*Diuretic Measures Used in Addition to Dietary Regimen, Diuretic Salts and Acacia for Thirty-Three Patients (Thirty-Eight Hospital Admissions) with Uncomplicated Nephrotic Edema, Successfully Treated*

Therapy	Number of Hospital Admissions in Which Used	Percentage of Hospital Admissions
Salyrgan	11	29
Esidrone	2	5
Desiccated thyroid gland	4	11
Paracentesis	1	3
Transfusion	4	11
Theocalcin	1	3
Aminophylline	2	5
Any form of diuretic therapy in addition to dietary regimen, diuretic salts and acacia	18	47
No therapy other than dietary regimen, diuretic salts and acacia	20	53

TABLE 6.—*Results of Combined Regimen of Treatment Including Injections of Solution of Acacia in Forty Consecutive Cases of Nephrotic Edema*

Status Obtained	First Hospital Admissions		Total Hospital Admissions	
	Number	Per Cent	Number	Per Cent
Entirely, or nearly free of edema at time of dismissal from hospital	36*	90	41	82
Status of edema essentially unchanged during period of hospitalization	4	10	9	18
Death (during period of hospitalization)	None	..	..	..
Total	40	100	50	100

* One of these patients, one year after his dismissal from the hospital free of edema, was found to have normal urine, normal blood and normal renal function. This case of complete clinical remission is discussed in more detail in the text.

and acacia were not given additional diuretic agents. Mercurial diuretics were administered in about a third of the cases, and, judging from the diuretic response obtained, the usefulness in most cases appears questionable. Thus, in the course of 13 patients admitted to the hospital (table 5), for whom injections of salyrgan or of esidrone (the sodium salt of pyridinedicarboxy-β-mercuri-ω-hydroxypropylamide-theophylline) or of both (on different occasions) were employed, the diuretic response was excellent in only 1, fair in another and in the remaining 11 either barely noticeable or absent.

Of the other diuretics employed, aminophylline was given intravenously, mixed with dextrose. In 2 cases treatment was complicated by comparatively advanced degrees of renal insufficiency. Theocalcin has been mentioned in table 5 because it has possible diuretic qualities. The direct indication for its administration, however, was diffuse arteriolar disease with hypertension superimposed on the original renal lesion.

In 1 case a transfusion of 500 cc. of blood was followed by an increase of the output of urine, amounting to 2,800 cc. in the ensuing

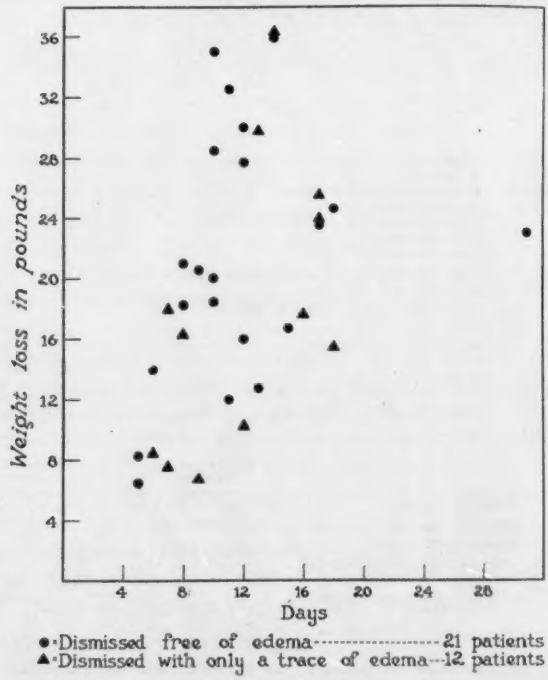

Chart 2.—Relation of time to loss of weight and summary of observations on the first hospitalizations of 33 patients who had an uncomplicated nephrotic type of edema and who were treated successfully with acacia. The average weight lost by 15 patients was 2 pounds (0.9 Kg.) or more per day; the average weight lost by 13 patients, 1 to 2 pounds (0.5 to 0.9 Kg.) per day; the average weight lost by 5 patients, less than 1 pound (0.5 Kg.) per day. Loss of weight due to mechanical elimination of fluid, e. g., by paracentesis or thoracentesis, has been subtracted. Thus the loss of weight represents the net weight lost through physiologic channels.

twenty-four hours. In other instances no beneficial effect on the edema was noticed. Thyroid has been used in an occasional case, but in this series we have not noted any beneficial effects from its administration.

Paracentesis has been advised for patients who have much mechanical embarrassment and who do not respond readily to diuretic treatment. As can be seen, its incidence in the present series was comparatively low. Thus, as a whole, additional diuretic measures appear to be of relatively little value as a supplement to the treatment with diet, diuretic salts and acacia.

Results.—The results of the combined regimen of treatment, including injection of acacia, in 40 consecutive cases of nephrotic edema are summarized in table 6. It is evident that 90 per cent of the patients, at the time of their first admission to the hospital, could be relieved of edema. Some reasons for failure of treatment of the remaining 10 per cent will be considered later in this paper.

The rate at which the edema disappeared has been represented in chart 2. It is evident that, on an average, weight (edema fluid) was lost at a rate of between 1 and 2 pounds (0.5 and 0.9 Kg.) per day. Even in those cases in which the response was relatively slow, a loss of nearly 1 pound (0.5 Kg.) per day occurred.

REPORT OF CASES

CASE 1.—This case has been mentioned earlier.

CASE 2.—A boy 15 years of age was admitted to the clinic on July 5, 1938. In May 1938 he had had a cold of negligible severity, unaccompanied by a sore throat. A few days later, however, he had noticed edema around the ankles, soon followed by puffiness around the eyelids. Urinalysis elsewhere revealed marked albuminuria and a few erythrocytes in the urine. He was put to bed for five weeks, fluid was restricted and a low salt diet was prescribed. The edema, however, did not diminish. When the patient was admitted to the clinic few symptoms were noted other than those already enumerated. Fluid in the abdomen was not demonstrable. The blood pressure was 125 systolic and 75 diastolic. Examination of the ocular fundi gave negative results. The volume of urine for twelve hours was 200 cc.; the specific gravity was 1.034. Urinalysis revealed albumin, grade 4, and granular casts, grade 3 plus, but no erythrocytes. On admission the concentration of urea was 60 mg.; that of cholesterol, 490 mg., and that of serum proteins, 3.9 Gm. per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.14, and the colloid osmotic pressure of the serum was 66 mm. of water. Because of the pus noted occasionally in the urine, a urologic investigation was made. This, including an excretory urographic study, gave entirely negative results. A diagnosis of subacute glomerulonephritis with nephrotic features was made.

The course in the hospital is illustrated in chart 3. The patient was given a salt-free diet with 70 to 75 Gm. of protein daily; fluids were limited to 1,000 cc. per day. Potassium nitrate, 9 Gm. daily, was also prescribed, and potassium chloride was allowed as a substitute for salt. A course of injections of acacia was started on the second day. However, after having received 100 cc. the patient complained of some substernal pain and dyspnea, and the injection was discontinued. One grain (0.06 Gm.) of codeine sulfate was administered, with prompt subsidence of the unpleasant symptoms. Three days later the patient was able to tolerate 500 cc. of a 6 per cent solution of acacia without any undesirable effects. On the fifth day he had started to lose weight and, continuing his progress, was

practically free of edema on the eleventh day, after having lost approximately 30 pounds (13.6 Kg.).

One day after the last injection of acacia the concentration of serum proteins was 3.1 Gm. per hundred cubic centimeters and the colloid osmotic pressure 91 mm. of water. During treatment in the hospital, the value for blood urea decreased to 40 mg. per hundred cubic centimeters, and three months later it was 24 mg. The patient was dismissed on the fifteenth day of hospitalization, free of edema and feeling very well. He was advised to continue the salt-free diet with 70 to 75 Gm. of protein, to restrict the intake of fluid to 1,000 cc. and to take 7.5 Gm. of potassium nitrate per day.

The regimen followed in this case proved satisfactory and is the usual one employed in this type of case. Seldom are other diuretic measures necessary.

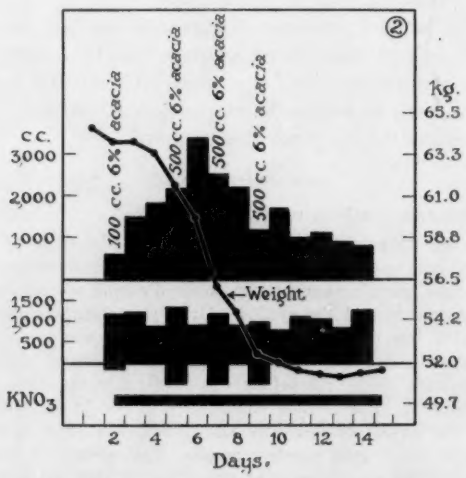

Chart 3 (case 2).—Essential factors of fluid balance in the case of a patient with nephrotic edema whose treatment consisted of special diet, restriction of fluids and administration of potassium nitrate (9 Gm. daily) and acacia. This is a typical graph of an uncomplicated course in which prompt response to the regimen occurred. The details of the chart are explained in the legend of chart 1.

Case 3.—A white man aged 30, single, had noted painless edema of the legs and ankles for nine months, since January 1938. He also had noted a scanty volume of urine and had been told elsewhere that his urine contained a considerable amount of albumin. On his admission (August 6) extensive edema of the lower extremities as far as the hips was noted. The blood pressure was normal, and examination of the ocular fundi gave essentially negative results. The urine had a specific gravity of 1.023 and contained albumin, grade 4. Bence-Jones protein was not present; there were hyaline casts, grade 2 (on the basis of 1 to 4), granular casts, grade 2 (on the basis of 1 to 4) and erythrocytes, grade 1 (on the basis of 1 to 4). The concentration of urea was 44 mg.; that of cholesterol, 877 mg. and that of serum proteins, 3.9 Gm., per hundred cubic centimeters

of blood. The albumin-globulin ratio was 1:1, and the colloid osmotic pressure of the serum was 110 mm. of water. The diagnosis was chronic glomerulonephritis of the nephrotic type, with massive edema.

The patient was placed in the hospital (chart 4) on our standard regimen, and after the third day the edema began to disappear. Acacia was administered on four consecutive days, together with 9 Gm. of potassium nitrate per day; this brought the daily volume of urine up to 2,400 cc. Salyrgan was given on the second day following admission, after the urinary output was 1,100 cc. for twenty-four hours; on the next day without any diuretic measures except administration of potassium nitrate, the volume of urine amounted to 1,600 cc. On the eighth day of the patient's stay in the hospital another injection of salyrgan was given. Although the resulting output of urine amounted to 2,000 cc. in twenty-

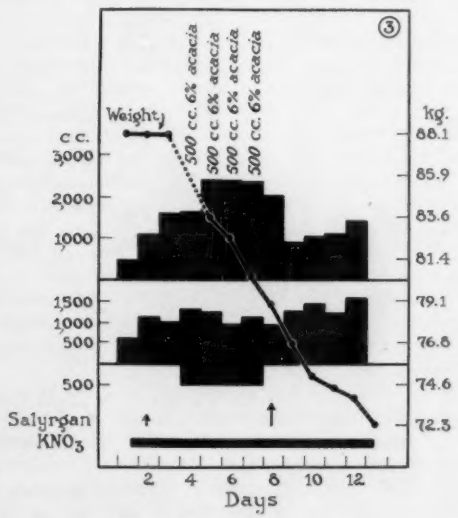

Chart 4 (case 3).—Essential factors of fluid balance in the case of a patient with nephrotic edema treated by the standard regimen supplemented with 9 Gm. of potassium nitrate daily. Notice the slight diuretic response to salyrgan before acacia was given and the good volume of urine after the use of acacia. Successive days without salyrgan, however, show volumes of urine each twenty-four hours even larger than those with salyrgan. Thus, considering the course in the hospital as a whole, salyrgan did not add much to the regimen of diet, potassium nitrate and acacia. The details of the chart are explained in the legend of chart 1.

four hours, this was less than the diuresis which occurred on the days following administration of acacia. The patient was dismissed from the hospital on the thirteenth day, free of edema, and was advised to continue the regimen outlined.

This case illustrates two points previously mentioned. One is that in the majority of cases salyrgan does not add much to the effectiveness of treatment with diet, potassium nitrate and acacia. This is

brought out by the fact that the volume of urine secreted after the first administration of salyrgan, although larger than on the previous day, was not as large as on the following day, when salyrgan was not given, nor was the volume on the day of the second administration of salyrgan as large as on the three previous days, although it was considerably in excess of the volume for the subsequent day. Another important point is that this case illustrates the fact described by us, as well as by Landis, that diuretics appear to give better results after acacia has been given than before.

CASE 4.—A white sailor aged 39 registered at the clinic Dec. 17, 1937. He stated that in his work he had been exposed to frequent chilling and that in 1933, when he had a cold, he had noticed some puffiness under his eyes. At that time his physician had found albumin in the urine. The patient had stayed in bed for five days. In 1935, however, he had passed a life insurance examination. Later in the same year he had an experience similar to the one in 1933; the symptoms lasted only a few days. Two months before his registration at the clinic, after exposure to rather extreme conditions of moisture and cold, he had noticed puffiness of the ankles. On the fourth day he had felt sick, and on the fifth day he had noticed puffiness "all over." He was hospitalized elsewhere for five weeks and was put on a low salt diet with restriction of fluid to 1,000 cc. a day. Nevertheless, he gained 25 pounds (11.3 Kg.) during that period. After leaving the hospital, treatment with a high protein diet and administration of 2 Gm. of thyroid extract three times daily had failed to improve his condition. One week before admission to the clinic the patient had been given an intramuscular injection, probably a mercurial diuretic, followed by an output of 4,200 cc. of urine in the first twenty-four hours; a diuretic effect of lesser degree persisted for three more days.

Examination at the clinic revealed slight puffiness of the eyes and extensive edema of both legs. The blood pressure was 175 mm. of mercury systolic and 100 mm. diastolic. Examination of the ocular fundi gave essentially negative results. The urine had a specific gravity of 1.022. There were albumin, grade 4; hyaline casts, grade 1; granular casts, grade 2; erythrocytes, grade 1 and leukocytes, grade 2. The concentration of urea was 30 mg., that of cholesterol, 792 mg., and that of serum proteins, 4.0 Gm. per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.2, and the colloid osmotic pressure was 89 mm. of water. The blood urea clearance amounted to 23.4 cc. per minute, at a volume of 15 cc. per hour. A diagnosis was made of chronic glomerulonephritis of the nephrotic type, with edema.

The course of this patient in the hospital is illustrated in chart 5. The scheme of treatment was essentially the same as that in cases 2 and 3. A few days after completion of the course of acacia, the colloid osmotic pressure of the serum was 93 mm. of water, and the serum contained 1,500 mg. of acacia per hundred cubic centimeters. The patient was dismissed from the hospital, free of edema, on the fourteenth day and was advised to continue on a low salt diet, to limit the intake of fluid to 1,000 cc. daily and to take 100 Gm. of protein a day and 2.5 Gm. of potassium nitrate three times a day for five days in each week.

One month after his dismissal, the patient returned for reexamination. He had gained 4 pounds (1.8 Kg.), and some edema of the legs was present. The specific gravity of the urine was 1.036; there were albumin, grade 4, hyaline casts, grade 1, and erythrocytes, grade 1. The concentration of urea was 38 mg.

and that of serum proteins 3.2 Gm. per hundred cubic centimeters of blood. The blood urea clearance amounted to 54.9 cc. per minute at a volume of 340 cc. per hour. The colloid osmotic pressure of the serum was 76 mm. of water. The patient was given two more injections of acacia, which raised the colloid osmotic pressure to 106 mm. of water and the concentration of acacia in the serum from 1,240 to 1,860 mg. per hundred cubic centimeters. The patient was advised to continue the regimen as outlined.

One year later, in January 1939, he returned to the clinic for reexamination. He stated that he had been able gradually to cut down the amount of potassium nitrate taken, while remaining free of edema. He was feeling very well. General examination gave negative results, and his weight was the same as the weight

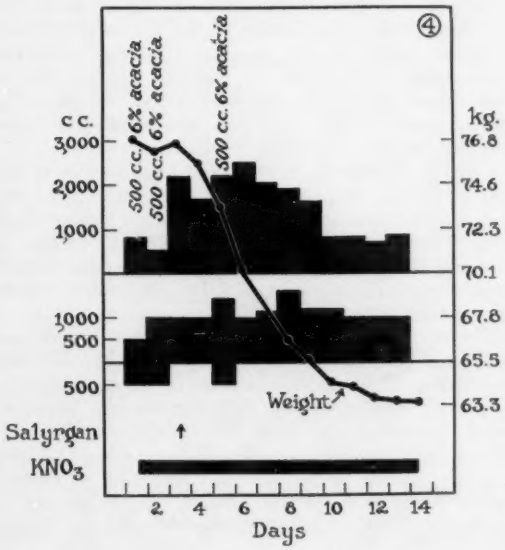

Chart 5 (case 4).—Essential factors of fluid balance in the case of a patient with nephrotic edema who made a complete recovery (clinical cure) subsequent to dismissal from the hospital. He was given potassium nitrate, 9 Gm. daily, and salyrgan, 1 cc. (intravenously), with fairly good response. Clinically, the course in the hospital was not different from that of the other patients described. The details of the chart are explained in the legend of chart 1.

recorded on his dismissal from the hospital. The specific gravity of the urine was 1.030; albumin was not present. The concentration of urea was 38 mg. per hundred cubic centimeters of blood; the blood urea clearance amounted to 73 cc. per minute at a volume of 440 cc. per hour. The concentration of serum proteins was 7.5 Gm. per hundred cubic centimeters, and the colloid osmotic pressure of the serum was 405 mm. of water.

The complete clinical remission in this case was certainly gratifying. It allows one to look somewhat more optimistically on the many cases

in which a diagnosis of chronic glomerulonephritis with predominant nephrotic features appears the one best suited to the history and the pathologic picture. We realize that the diuretic measures employed cannot be held directly responsible for this remarkable remission; however, the clinical course definitely shows that treatment with acacia does not interfere with healing processes in the kidney.

CASE 5.—A white man aged 38 was admitted to the hospital Jan. 3, 1939, because of recurrence of swelling of the legs for the previous two weeks.

He had been hospitalized by physicians at the Mayo Clinic ten weeks previously, at which time a diagnosis of chronic glomerulonephritis with nephrotic features had been made. At that time he had completed successfully the standard treatment with a low salt diet, potassium nitrate and acacia and had lost 16 pounds (7.3 Kg.) in twelve days. He had been dismissed free of edema and was instructed to continue with his special diet, potassium nitrate and restriction of fluids. However, after approximately six weeks he had experienced gastrointestinal symptoms, and the administration of potassium nitrate was discontinued. It was at this time that the patient had noticed recurrence of edema.

At the time of his readmission to the hospital the content of acacia in the serum amounted to 225 mg. per hundred cubic centimeters, which was approximately 15 per cent of the estimated concentration at the end of the first period of hospitalization. The concentration of serum proteins was 3.1 Gm. per hundred cubic centimeters, and the albumin-globulin ratio was 1.1:1. On his first admission the concentration of plasma proteins was 3.4 Gm. per hundred cubic centimeters and the albumin-globulin ratio was 1:1.1.

Diuretic salts were not administered until the eighth day of hospitalization (chart 6). The patient received the standard diet, and on the third day treatment with acacia was started. Abundant diuresis promptly ensued, and in five days the patient lost 14 pounds (6.4 Kg.). One day, after the third injection of acacia, the colloid osmotic pressure of the serum was 95 mm. of water, and the serum contained 1,770 mg. of acacia per hundred cubic centimeters. Addition of potassium chloride to the regimen at this time had essentially no further effect. A final dose of acacia on the tenth day was followed again by diuresis. The patient was dismissed, free of edema, on the fourteenth day after his entrance into the hospital.

As was stated earlier in this paper, the most efficient treatment of the patient who has a nephrotic type of edema incorporates dietary measures and administration of potassium nitrate and acacia. Even though particularly striking results can be obtained with otherwise resistant nephrotic edema, one is justified in questioning for a moment the essential value of acacia in a complicated regimen like this. However, in case 5, potassium nitrate was not well tolerated, and its omission from the regimen supplied us with an interesting experiment in obtaining evidence of diuretic action of acacia without benefit of diuretic salts. In case 6 a prolonged regimen with potassium nitrate was supplemented with occasional injections of acacia and thus gave us additional opportunity to study the effects of the acacia itself. The results in case 5

support the view that acacia has properties by which it definitely facilitates the mobilization of fluid and its elimination in the urine in the nephrotic type of edema. The colloid osmotic pressure, however, at the time when diuresis was taking place efficiently was considerably subnormal.

Case 6.—A white painter aged 47 registered at the clinic April 13, 1939. He stated that in September 1938 he began to experience rather frequent severe headaches. His blood pressure at that time was 182 mm. of mercury systolic and 120 mm. diastolic. In January 1939 severe pitting edema of the ankles had developed. Examination elsewhere showed a severe degree of albuminuria. Toward the end of February he had contracted influenza, and he noted a considerable increase in the amount of edema. Later the abdomen appeared to be swollen. On examination,

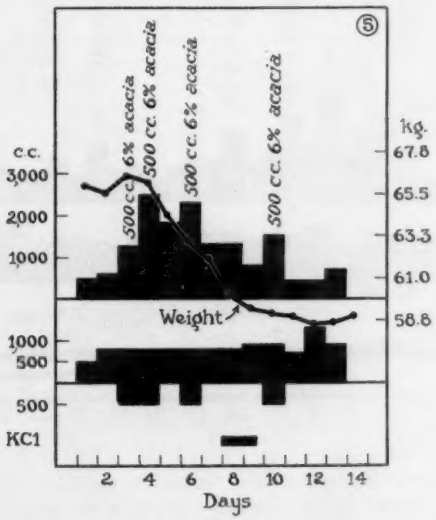

Chart 6 (case 5).—Essential factors of fluid balance in the case of a patient with nephrotic edema. The marked diuretic effect of acacia without simultaneous administration of potassium salts is obvious; the patient lost 13.5 pounds (6.1 Kg.) in five days. Additional loss of 2.5 pounds (1.1 Kg.) made the patient entirely free of edema on dismissal from the hospital. The details of the chart are explained in the legend of chart 1.

puffiness of the eyelids was noted; the second aortic sound was accentuated; ascites (grade 1 to 2) was present, and rather extensive edema of the lower extremities was noted. The ocular fundi showed extensive retinitis of the acute angiospastic type, with a great deal of "cotton-wool" exudate, hemorrhages and some edema, a condition similar to the angiospastic retinitis associated with chronic glomerulonephritis. The urine had a specific gravity of 1.028 and contained albumin, grade 4; casts, grade 3, and erythrocytes, grade 1. The concentration of urea was 69 mg.; that of cholesterol, 536 mg., and that of serum proteins, 3.7 Gm., per

hundred cubic centimeters of blood. The albumin-globulin ratio was 1 : 1.2 and the colloid osmotic pressure of the serum was 73 mm. of water. A diagnosis of chronic glomerulonephritis with nephrotic features and superimposed diffuse arteriolar disease with hypertension was made. After treatment in the hospital (chart 7), during which the colloid osmotic pressure of the serum rose to 114 mm. of water, he was dismissed, with only a slight residual edema, on the twenty-fifth day of hospitalization and was advised to continue the hospital regimen. He was last heard from July 22, at which time he stated that he had lost 6 pounds (2.7 Kg.) after leaving the hospital, and that he was feeling very well and doing a limited amount of work without noticing any ill effects.

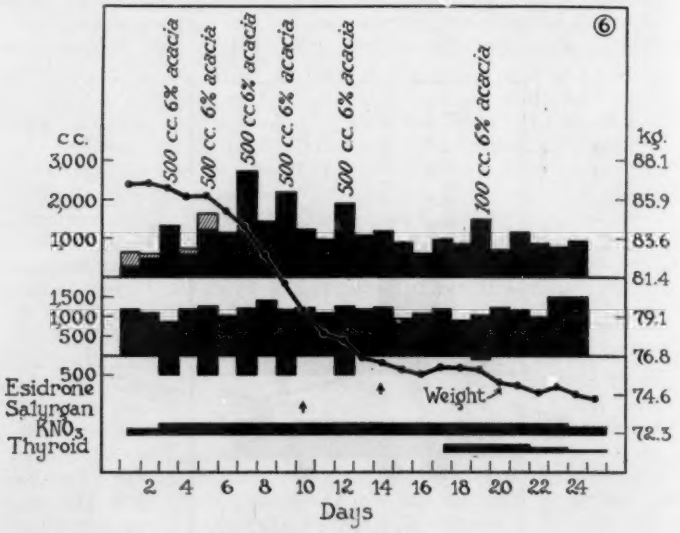

Chart 7.—Essential factors of fluid balance in the case of a patient with nephrotic edema, treated by the standard regimen in the hospital. The patient received potassium nitrate, 10 Gm. in the first two days combined and then 12 Gm. per day until the last two days, when the dose was 8 Gm. daily, and, desiccated thyroid gland, starting on the seventeenth day, 4½ grains (0.29 Gm.) daily, the dose being soon reduced to 3 grains (0.2 Gm.) and 1½ grains (0.1 Gm.) respectively. Neither salyrgan (1 cc.) nor esidrone (1 cc.) was followed by an appreciable diuretic response. The chart illustrates how each injection of acacia was followed by a definite diuretic response, while the dietetic treatment and the amount of potassium nitrate given daily remained essentially constant throughout the period of hospitalization. The details of the chart are explained in the legend of chart 1. The cross-hatched blocks on top of those that represent the volume of urine indicate the volume of output by emesis.

The increased output of urine following each injection of acacia is remarkable and, in view of the constancy of the other therapeutic measures, points definitely to the beneficial properties of acacia itself.

Mercurial diuretics did not appear to increase the rate of disappearance of edema under the regimen employed.

In the following 3 cases the edema was of multiple origin. Acacia was employed in the treatment.

CASE 7.—A woman 53 years of age was known to have had chronic glomerulonephritis for many years and renal insufficiency for some years. In addition, she was suffering from myocardial degeneration and insufficiency, which had been responsible for keeping her in bed most of the time for the past few years. In addition, at the time of admission to the hospital (in September 1938) secondary diffuse arteriolar disease with hypertension was developing. She had albuminuria, grade 4. The concentration of urea was 84 mg.; that of cholesterol, 315 mg., and that of serum proteins 4.7 Gm., per hundred cubic centimeters of blood. The albumin-globulin ratio was 1.9 : 1, and the colloid osmotic pressure of the serum was 149 mm. of water. The blood urea clearance was 30.6 cc. per minute at a volume of 170 cc. At home the patient had been treated for a long time with digitalis and potassium nitrate in addition to being placed on a salt-free diet and permitted a limited intake of fluids. However, a moderate amount of edema was present on admission. After treatment with acacia (90 Gm. in five days) she became free of gross evidence of edema, and the colloid osmotic pressure of the serum increased to 161 mm. of water.

In view of the other treatment administered, which consisted of administration of digitalis, aminophylline and potassium nitrate, it is difficult to evaluate the exact role which the acacia played in clinical recovery of the patient. However, it would appear that the increased colloid osmotic pressure would have facilitated the flow of fluid from the tissues to the blood. It is especially noteworthy that the blood pressure, measured before breakfast every morning, did not increase after the use of acacia. Equally remarkable is the fact that, although part of the patient's edema was clearly due to myocardial insufficiency, undesirable effects from the increase in blood volume which always follows the administration of acacia were not noted.

CASE 8.—A man 59 years of age was suffering from diffuse arteriolar disease with hypertension group 3 (according to the classification of Keith, Wagener and Barker [21]), coronary sclerosis, generalized arteriosclerosis, myocardial degeneration and decompensation and chronic glomerulonephritis with nephrotic features. Albuminuria, grade 4, was present. The concentration of urea was 38 mg.; that of cholesterol, 321 mg., and that of serum proteins, 4.1 Gm., per hundred cubic centimeters of blood. The albumin-globulin ratio was 1 :1.1, and the colloid osmotic pressure of the serum was 88 mm. of water. The patient was treated in the hospital with the standard diet; fluids were restricted, and 9 Gm. of potassium nitrate was administered daily. In addition to this, 1 cc. of salyrgan was given on two different days, with only slight diuretic effect, so that in nine days in the hospital the patient had lost only 3 pounds (1.3 Kg.). At this time

21. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332-343 (March) 1939.

acacia was administered, a total of 84 Gm. in five days. He lost 8 pounds (3.6 Kg.) in the next five days, and at the end of this period was clinically free of edema. Salyrgan had not been used since the treatment with acacia had been started, and digitalis had not been employed during the entire period of hospitalization. The patient was dismissed from the hospital without edema.

Again it appears that although myocardial insufficiency was present, acacia had a definite part in relieving the patient's edematous state. The severe albuminuria, the low concentration of serum proteins, the inversion of the albumin-globulin ratio and the low colloid osmotic pressure leave little doubt that the patient, in addition to diffuse arteriolar disease with hypertension, was suffering from a nephrotic type of lesion and that part of the edema was due to the latter condition. Certainly the patient responded much better to acacia than to salyrgan, although treatment otherwise remained unchanged, which in turn possibly might be considered an indication of the nephrotic origin of the edema.

CASE 9.—A man aged 27 had undergone splenectomy in 1931 because of splenic anemia; he had been in good health after the operation. In January 1937, after a severe attack of influenza accompanied by a sore throat, on getting out of bed he had noticed that his ankles were swollen. At that time much albumin and some erythrocytes were found in the urine. On admission to the clinic (December 12) physical examination gave essentially negative results except for a slight but definitely noticeable amount of ascites, considerable edema of the legs and some edema over the sacrum. The concentration of urea was 28 mg.; that of cholesterol, 641 mg., and that of serum proteins, 5.3 Gm., per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.4, and the colloid osmotic pressure of the serum was 147 mm. of water. The blood urea clearance was 43.3 cc. per minute at a volume of 32 cc. per hour. Hepatic function, according to the results of galactose tolerance, hippuric acid and dye retention tests, was normal. The patient was given the standard treatment with potassium nitrate and acacia, and he lost 14.2 pounds (6.5 Kg.) in eight days. He was dismissed from the hospital free of edema.

When the patient returned for reexamination, in October 1938, he again had some edema, although the concentration of serum proteins had increased to 6.7 Gm. per hundred cubic centimeters. At this time, a few prominent veins were noted on the abdomen. The colloid osmotic pressure of the serum was 211 mm. of water. In February 1939 some degree of ascites and dependent edema, in part controlled by the dietary measures, was present. Never during the course of his illness was any accumulation of fluid above the diaphragm noticed.

In this case, the concentration of serum proteins and the colloid osmotic pressure were never very low, and even after they had increased the ascites and dependent edema could not be controlled at all times. In view of the related history and the presence of prominent veins over the abdomen, it was assumed that some degree of obstruction of the portal circulation, possibly in combination with obstruction of flow in the inferior vena cava, had taken place. Thus, probably the edema ever since it first appeared had been of mixed origin. Nevertheless, response to acacia was prompt and satisfactory.

ACACIA IN THE NEPHROTIC SYNDROME WITHOUT EDEMA

As has been stated earlier in this study, patients in whose cases the laboratory data denote the nephrotic syndrome may or may not have actually manifest edema. Some may have only slight degrees of edema which may be controlled with diet alone or with diet supplemented by interrupted courses of potassium or ammonium salts. Usually the colloid osmotic pressure, although decreased, is not as greatly reduced as in cases in which severe degrees of edema exist.

In the last two years at the Mayo Clinic, acacia has been administered to 10 patients who had the nephrotic syndrome but practically no edema. Since edema was not present, it is difficult to judge the success of what might be called "prophylactic" treatment with acacia. One of the objects of this treatment has been to enable patients who have a tendency toward formation of edema, decreased renal function and retention of urea in the blood to take somewhat larger amounts of fluid than is customary. In a number of instances we have seen definite decreases in the concentration of blood urea following the use of acacia. Some patients without renal insufficiency have indicated that they could tolerate a larger intake of fluid after injection of acacia. There never was an unfavorable influence either on the concentration of urea in the blood or on the blood pressure. However, more experience is necessary before a final opinion can be expressed about the merits of administration of acacia to patients who have the nephrotic syndrome without edema.

LIMITATIONS OF EFFECTIVENESS OF COMBINED THERAPY

In 4 of a total of 40 cases the combined form of treatment proposed did not lead to satisfactory diuresis. In addition, 3 patients who at one time responded well were not controlled satisfactorily during a relapse. One of these, readmitted to the hospital a few weeks later, lost edema rather promptly. The case of this patient is especially interesting in that at the time of the first admission the colloid osmotic pressure of the serum was 145 mm. of water; at the time when treatment was of no avail, it was 72 mm., and when treatment was effective again, it was 116 mm. Nevertheless, in 1 case in which the edema was rapidly relieved the colloid osmotic pressure of the serum before treatment with acacia was only 62 mm. of water, and even after completion of the course of injections of acacia it increased only to 67 mm.

In reviewing the cases in which treatment for reduction of edema was unsuccessful, we find that there are several probable causes of failure. They include (1) anorexia and vomiting, (2) insufficient amounts of diuretic salts and (3) insufficient amounts of acacia.

The cause of the anorexia and vomiting occasionally observed in patients with nephrotic edema is not well understood at present. Exam-

inations of the gastrointestinal tract in these cases, as well as tests of hepatic function gave negative results throughout. In this respect the condition in these cases may be thought to simulate anorexia nervosa and nervous vomiting. However, the symptoms are more likely to be secondary to the renal disease itself. The reduced intake of food results in malnutrition, and a vicious cycle is thus established. Resolution of the edema is further hampered by inability to ingest the necessary amounts of diuretic salts. The seriousness of the condition is illustrated well by the fact that of the 4 patients 3 are known to have died since their dismissal from the hospital, and we have not been able to reestablish contact with the fourth. The most rational attack on the problem might well incorporate parenteral administration of all nutritional and therapeutic materials which are not tolerated by mouth. The need for treatment of patients with this condition is all the more urgent because it is known that once they have been liberated of edema appetite returns, morale improves and the vicious cycle is broken.

Diuretic salts should be given in all cases for a sufficient period and in sufficient dosage. Their administration for two or three days should precede injection of acacia if one is to expect optimal results. Premature discontinuance in the occasional case definitely jeopardizes the ultimate success of the combined form of treatment.

In many cases of the severe types of nephrotic edema much acacia is lost in the urine, and it is difficult to reach an optimal concentration in the body. The dosage of acacia, at present, is mostly on an empiric basis. Thus, in rare cases larger doses than those recommended in this paper may well be necessary.

COMMENT

General Considerations.—The nephrotic syndrome is characterized by albuminuria, hypercholesteremia, a low concentration of serum proteins and a low colloid osmotic pressure of the serum. The last two factors generally are considered directly responsible for the edema, without which the syndrome is usually asymptomatic. The composition of the edema fluid, which contains only a small amount of protein, corresponds closely to an ultrafiltrate of serum, being essentially an isotonic solution of sodium chloride and other ions. It accumulates in excess in the tissue spaces.

The large amount of albumin excreted in the urine is derived from the proteins of the serum, largely from the albumin fraction, and this constant drain is considered the main reason for the diminished amounts of protein found in the serum. Starling,[22] in 1896, published his experi-

22. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312-326, 1896.

ments on the rate of absorption of fluid from the subcutaneous tissues. He found that salt solutions were much more readily absorbed than were those containing proteins. This has led to our present conceptions of the exchange of fluid through the capillary membrane, the amount of fluid filtered through depending on the relation between the intravascular hydrostatic pressure, which tends to force fluid from the capillaries into the tissue spaces, and the colloid osmotic pressure of the serum proteins, which attracts fluids from the tissue spaces toward the lumens of the blood vessels. In accordance with this scheme, in conditions of hypoproteinemia and low colloid osmotic pressure of the serum the normal dynamic equilibrium will be displaced, so that a larger amount of fluid is expressed from the lumen toward the tissue spaces than is reabsorbed, and edema appears.

This mechanical conception loses its applicability as soon as the role of the kidney in the syndrome is studied. With oliguria as an essential part of the nephrotic edematous state, apparently the diminished water-binding power of the blood proteins does not make for an increased final volume of transudate (urine). Formerly, it was thought that the edema "deviated" fluid from the processes of urine formation (so-called prerenal deviation). But that conception is not in accordance with the newer views of renal function, which postulate for man a rate of glomerular filtration of the order of 150 cc. per minute; this value presumably is approximately as large in the true nephrotic state as it is in the normal, as is evidenced by the normal results of clearance tests in those cases of chronic nephrosis in which glomerulonephritic changes are absent.

No satisfactory explanation appears to exist at present for the small volume of urine with high specific gravity and low chloride content which is so characteristic of the edematous nephrotic state. However, the same situation presumably is encountered in cases of so-called nutritional edema and in cases of edema of undetermined origin, such as have been described by Binger and Keith.[23] An analogous state also may be produced in animals by the use of repeated plasmapheresis. The weight increases, and visible edema develops, presumably because water and salt are not excreted in sufficiently large quantities. The volume of urine is decreased even more if sodium chloride is administered orally at the same time.

Thus, in view of the analogous situation encountered among patients who have the nephrotic syndrome and other conditions of hypoproteinemic edema and in animals subjected to plasmapheresis, it appears that failure of the kidney to excrete water and sodium chloride in sufficient

23. Binger, M. W., and Keith, N. M.: General Edema of Indeterminate Etiology: Report of Three Cases, J. A. M. A. **109**:1-6 (July 3) 1937.

amounts is conditioned by decrease of the concentration of serum proteins or of the colloid osmotic pressure of the serum. This failure on the part of the kidney is only relative, since satisfactory diuresis often can be obtained without simultaneous increases of the colloid osmotic pressure of the serum. Such diuresis may be induced by a change in the ionic environment, such as occurs with the administration of potassium nitrate, or by a forceful change of tubular permeability, such as is effected by administration of mercurial diuretics or such as may occur during so-called spontaneous diuresis when the patient is maintained on a salt-free regimen.

On recognition of decrease of the colloid osmotic pressure of the serum as conducive to the development of edema (1) through the understandable mechanism of increased filtration and decreased reabsorption through the wall of the capillaries in the body at large, and (2) through the less well understood phenomenon of decreased elimination of chloride and water by the kidney, it appears imperative to foster attempts to remedy this deficiency. Four different types of treatment are usually employed, often more than one at the same time: a high protein diet, blood transfusion, administration of concentrated lyophil serum and injection of acacia.

At present, administration of a high protein diet is part of the generally accepted method of treatment of the nephrotic syndrome and should be utilized regardless of what other forms of treatment are being used. The futility of transfusions to bring about an increase in colloidal osmotic pressure of the serum is clear when it is realized that such procedures add to the blood stream an amount of protein equal to the amount which is being excreted every one to seven days in the urine in the type of case under consideration.

The first observations on the use of concentrated lyophil serum, published by Aldrich and his co-workers,[24] appear favorable. The amounts of serum proteins given exceed the ones present in the average transfusion, and the results appear definitely superior. Further experience with this form of treatment is being awaited with great interest, especially since an instance of very rapid and complete cure is cited in the original communication.

The administration of acacia may produce a temporary rise in the colloid osmotic pressure of the serum (Kerkhoff; Butt, Power and Keys; Peters). The substance remains within the circulation for extensive periods, although not as long in cases of nephrosis as in cases in which albuminuria is not present. These and other problems bearing

24. Aldrich, C. A.; Stokes, J.; Killingsworth, W. P., and McGuinness, A. C.: Concentrated Human Blood Serum as a Diuretic in the Treatment of Nephrosis: Preliminary Report, J. A. M. A. **111**:129-133 (July 9) 1938.

on the mechanism whereby acacia exerts its favorable therapeutic effect are being investigated at present and will be reported on later.

Clinical Considerations.—Clinically the results of treatment of nephrotic edema with acacia are highly satisfactory. Used in conjunction with a high protein, salt-free diet, restriction of fluid and administration of potassium nitrate, disappearance of the edema at a rate averaging between 1 and 3 pounds (0.5 and 1.3 Kg.) per day could be observed in 36 cases. The patients subsequently could be dismissed from the hospital free of edema or practically so. Of 40 consecutive patients hospitalized for treatment of a nephrotic type of edema, to whom acacia was administered when they were first admitted to the hospital, the treatment afforded efficient loss of edema in 36 (90 per cent). These figures cannot be compared with any others in the literature, because a comprehensive analysis of therapeutic results in a consecutive series of cases of nephrotic edema has not been published. The absence of such a study explains the vague and subjective presentation of the therapeutics of the nephrotic type of edema usually encountered.

A review of 7 cases in which, at one time or another, there was failure to respond to the described regimen of diuretic therapy revealed that in the majority of instances great difficulty had been encountered in having the patients take their diet and diuretic salts. In practically all cases potassium nitrate had not been given in the full therapeutic dose or over a sufficiently long period. Future advances in the treatment of nephrotic edema may well be centered in finding some modification of the present regimen which would not depend on the oral route for administration of nutritional and therapeutic essentials. However, it should be realized that probably no form or combination of treatments will ever be effective and successful in 100 per cent of cases.

Safety of Injections of Acacia.—Acacia can be given with comparative safety, and when it is used in combination with the other component parts of the recommended regimen its effective dose is so low that toxic effects from overdosage are not observed. Thus, administering a total amount of approximately 1.5 to 2 Gm. per kilogram of body weight in the course of three to six days has never given rise in our experience to enlargement of the liver, although we have been watching for it diligently. We have thought it advisable to refrain from repeating the course of treatment with acacia until a sufficient period had elapsed. Thus, in order to obtain the maximal benefit, one would do well to precede the injections of acacia by two or three days' treatment with diuretic salts.

In connection with the alleged damage to the liver, it is worth remembering that all of those investigators who have stressed this point

most used doses many times larger than those mentioned and recommended in the present study. Butt and Snell [25] found that acacia, the same preparation that we have used, in approximately the same dosage, is well tolerated by patients who have cirrhosis of the liver with ascites and that it does not provoke the appearance of clinical signs or symptoms suggestive of further impairment of hepatic function. These observations furnish additional valuable clinical evidence that under the regimen of treatment recommended acacia does not exert any harmful effect on the liver.

The decrease in concentration of serum proteins which is regularly observed after injections of acacia and which by some investigators is ascribed to damage of the liver can be explained most simply on the basis of dilution of the serum with the colloidal solution of acacia; certainly the decreases in values for serum protein on the one hand and in those for hemoglobin and hematocrit values on the other, such as are observed after a course of injections of acacia, are of comparable magnitude. Also, the decrease in concentration of serum proteins is greatest shortly after the injection of acacia, and a definite tendency toward an increase is noticeable from that time on. Such behavior does not appear to be compatible with the idea of hepatic dysfunction as the cause of the decrease in the concentration of serum proteins.

Thus, acacia is an effective therapeutic agent and is harmless if certain principles of preparation and administration are adhered to. Its inclusion in the regimen of the adult patient who has nephrotic edema, in addition to the usual dietary measures, and administration of diuretic salts in the great majority of instances give prompt and satisfactory results.

SUMMARY

Acacia can be incorporated advantageously into the regimen of treatment of the patient who has a nephrotic type of edema. Other therapeutic features should include the use of a salt-free, high protein diet, the restriction of fluids and the use of diuretic salts, preferably potassium nitrate. Of 40 successive adult patients treated according to these principles, all except 4 were promptly relieved of edema. Most often, failure of the treatment was due to inability of the patient to take sufficient nourishment and diuretic salts by mouth.

Diuretic salts are not essential, for acacia may produce diuresis when used in conjunction with diet alone. The best results, however, are most likely to be obtained if diuretic salts are included in the regimen.

Additional diuretic measures are seldom called for. Thus, except in a few instances, mercurial diuretics can well be dispensed with without

25. Butt, H. R., and Snell, A. M.: Personal communication to the authors.

sacrifice of therapeutic results. Sometimes diuretics ineffective before treatment with acacia become effective after such treatment.

Once proper attention is given to the preparation and administration of acacia, reactions after its injection are infrequent and mild. The dosage is important; the amount given in each course of treatment should be limited to 90 to 150 Gm. divided in daily doses of 30 Gm. Enlargement of the liver has not been observed at any time. In this fashion acacia may even be given to patients who have cirrhosis of the liver without further impairing hepatic function. The decrease in serum proteins observed after its injection can be accounted for adequately on the basis of increase in plasma volume and concomitant dilution of its constituents. Neither renal insufficiency, secondary vascular disease nor myocardial degeneration constitutes a contraindication to its use.

Thus, the addition of injections of acacia to a general regimen of treatment appears to provide efficient results for the patient who has a nephrotic type of edema.

CEREBRAL ABSCESS (PARADOXIC) ACCOMPANYING CONGENITAL HEART DISEASE

REPORT OF TWO CASES

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Cerebral abscess occurring in patients with congenital disease of the heart is rare and not commonly recognized. There are early recorded observations of cerebral abscess in patients dying with congenital heart disease, but it was not until 1880 that Ballet [1] first made clear the relationship of these two morbid conditions.

The incidence of congenital heart disease varies considerably in the necropsy observations reported from different institutions. For example, 75 cases of this anomaly reported by Leech [2] from the Johns Hopkins Hospital constituted 1.29 per cent of all the cases in which necropsy was done, whereas the 105 cases of congenital anomalies of the heart or the great vessels reported by Gibson [3] from the cardiac service of the Children's Memorial Hospital were 5.4 per cent of the 1,950 cases of infants on whom autopsy was performed. Cerebral abscess as a complication is not mentioned by either author. All the patients seem to have died from cardiac disease.

The term "paradoxic embolism" seems first to have been suggested by von Recklinghausen. Gowers [4] spoke of 2 or 3 cases of abscess of the brain in association with congenital heart disease. In 1912 Osler [5] stated that death of patients with congenital heart disease may be

From the Neurological and Neurosurgical Service of the Mount Sinai Hospital.

1. Ballet, G.: Des abscés du cerveau consécutifs à certaines malformations cardiaques, Arch. gén. de méd. **5**:659, 1880.

2. Leech, C. B.: Congenital Heart Disease: Clinical Analysis of Seventy-Five Cases from Johns Hopkins Hospital, J. Pediat. **7**:808-839 (Dec.) 1935.

3. Gibson, S., and Clifton, W. M.: Congenital Heart Disease: Clinical and Postmortem Study of One Hundred and Five Cases, Am. J. Dis. Child. **55**:761-767 (April) 1938.

4. Gowers, W. R: A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1888, vol. 2, p. 443.

5. Osler, W.: The Principles and Practice of Medicine, ed. 8, New York, D. Appleton and Company, 1912.

caused by abscess of the brain. In 1923 Abbott, Lewis and Beattie [6] collected 14 cases of paradoxic embolism. Six of these proved to be cases of cerebral abscess. Abbott's [7] study of 1,000 cases of congenital heart disease with associated patency of the foramen ovale, interventricular septum and ductus arteriosus contained 12 cases in which death occurred as the direct result of paradoxic embolism.

Four additional cases were found in the literature by Rabinowitz, Weinstein and Marcus,[8] and they reported 1 in which the abscess at autopsy was found in the cerebellum. Seven cases of paradoxic embolism observed at the Mayo Clinic were reported by Ingham,[9] in all of which the condition was associated with patent foramen ovale and preceded by pulmonary embolism. It is interesting that in 1 of these cases the patient presented sufficient localizing signs to warrant exploration of the left temporoparietal lobe for a cerebral abscess. Death followed on the thirteenth postoperative day. To our knowledge this is the first recorded case in which an attempt was made to drain a cerebral abscess following paradoxic embolism.

There is no adequate explanation of the mechanism of the production of "paradoxic" cerebral abscess accompanying congenital disease of the heart. In some cases there was a history of antecedent infection. For example, in cases 2 and 3 reported by Abbott, Lewis and Beattie there was evidence of an inflammatory focus shortly before the onset of the cerebral symptoms. In the case reported by Bach [10] the removal of carious teeth seemed to be the spark that started the symptoms. In the case reported by Ingham there was an infection of the upper respiratory tract three days before the onset of neurologic symptoms. Baumgartner and Abbott [11] were unable to locate the focus in their case of paradoxic embolism with cerebral abscess, yet they felt that sepsis in the lesser circulation must have been present. They stated the opinion that cerebral

6. Abbott, M. E.; Lewis, D. S., and Beattie, W. W.: Differential Study of a Case of Pulmonary Stenosis of Inflammatory Origin (Ventricular Septum Closed) and Two Cases of (*a*) Pulmonary Stenosis, and (*b*) Pulmonary Atresia with Associated Ventricular Septal Defect and Death from Paradoxical Cerebral Embolism, Am. J. M. Sc. **165**:636-659 (May) 1923.

7. Abbott, M. E.: Congenital Heart Disease, in Nelson's New Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1927, vol. 4, pp. 207-321.

8. Rabinowitz, M. A.; Weinstein, J., and Marcus, I. H.: Brain Abscess (Paradoxical) in Congenital Heart Disease, Am. Heart J. **7**:790-795 (Aug.) 1932.

9. Ingham, D. W.: Paradoxical Embolism, (with Patent Foramen Ovale), Am. J. M. Sc. **196**:201-207 (Aug.) 1938.

10. Bach, F.: A Case of Congenital Morbus Cordis Studied Over a Period of Twelve Years, Lancet **1**:1009-1011 (May 19) 1928.

11. Baumgartner, E. A., and Abbott, M. E.: Interventricular Septal Defect with Dextroposition of Aorta and Dilatation of the Pulmonary Artery ("Eisenmenger Complex") Terminating by Cerebral Abscess, Am. J. M. Sc. **177**:639-647 (May) 1929.

abscess is especially liable to occur when there is a defect in the ventricular septum as well as a dextroposition of the aorta. This combination seems to favor a direct path for the transmission of a crossed embolus. Another possible explanation is that vascular disease of the

Outstanding Findings in Reported Cases of Cerebral Abscess Associated With Congenital Heart Disease

Author	Age, Years, and Sex	Symptoms	Signs	Duration of Illness	Location of Abscess
Ferre, J. R.	9½ M	Headache, fever	Left hemiplegia	4 days	Right hemisphere
Bertody, Charles	21 F	Headache, delirium, fever, coma	.....	.....	Left posterior hemisphere and left ventricle
Stone, W. H.	10 F	.....	.....	.....	Right occipital lobe, right ventricle
Deneke, T.	18 M	Headache	Left hemiplegia	10 days	Right cerebral hemisphere, streptococci
Abbott, Lewis and Beattie	11 M	Headache, fever	Right hemiplegia	2 days	Left frontal lobe, purulent meningitis
Raab, William	15 M	Headache, fever	Left hemiplegia	3 weeks	Right hemisphere, purulent meningitis
Bach, Frances	30 M	Headache, fever, coma	.....	1 day	Right temporal lobe, purulent meningitis
Baumgartner and Abbott.	20 M	Headache, drowsiness, coma	Papilledema, left hemiplegia, left facial weakness; increased spinal fluid pressure, 9 cells	17 days	Right frontoparietal area, 5 cm. in diameter
Ballet, G.	15 M	.....	Left hemiplegia	10 days	Frontal lobe, purulent meningitis
Lullenand	57 F	.....	Left hemiplegia	10 days	Frontal lobe, purulent meningitis
Rabinowitz and others	16½ F	Fever, headache vomiting	.....	7 days	Cerebellum
Ingham	30 F	Right side of face and right hand numb, twitching right arm	.....	.....	Left hemisphere
Wechsler, I. S., and Kaplan, A. (present study)	14 M	Convulsion, headache, vomiting	Numbness on left side of body, papilledema, left facial paralysis and left hemiparesis	64 days	Right parietal lobe
Wechsler, I. S., and Kaplan, A. (present study)	11½ F	Headache, convulsion	Left facial paralysis, left hemiplegia	48 days	Right frontal lobe

brain together with consequent encephalomalacia prepares a focus which is receptive to infection, and if by chance organisms circulate in the blood they may cause the formation of an abscess.

In previous reports on this subject stress has been placed on valvular and vascular defects and anomalies. Comparatively little attention has been focused on the cerebral complication. With the lesion in the brain localized, the diagnosis generally is thrombosis or embolism.

The object of this report is to recall the fact that unheralded cerebral abscess may occur in persons with congenital heart disease and to point out that the abscess, which generally is single, should be drained.

In tabular form a review of the 12 collected cases from the literature of cerebral (paradoxic) abscess associated with congenital heart disease is presented. Particular note should be taken of the short duration of the illness, and also of the fact that the complication of cerebral (paradoxic) abscess is most frequent in those cases in which there are signs pointing to the tetralogy of Fallot. It is worth noting that 10 of the 14 abscesses occurred on the right side of the brain. Actually it is 10 out of 13, as 1 was in the cerebellum. What significance this has is difficult to say. One explanation which suggests itself is that the dextroposition of the aorta may in some way be responsible. This would be based on the assumption that an embolic process precedes the formation of the abscess.

REPORT OF CASES

Case 1.—D. G., a 14 year old school boy, was first admitted to the Jewish Hospital (Brooklyn) on July 25, 1935 because of convulsions of two weeks' duration.

The family history was irrelevant. At birth the patient was a "blue baby," and from the beginning he was recognized as having congenital cardiac disease. He had measles, mumps and chickenpox without complications. Two months before admission to the hospital he had an attack of influenza. He was guarded in his daily activities, and had advanced to high school.

Two weeks before admission he was suddenly seized with a convulsion which was regarded as an epileptic fit. Three days later he had another seizure, which involved the left side of the face, neck, arm and trunk, and he immediately lost consciousness. Shortly after the second convulsion he complained of pain in the right eye and numbness of the left side of the face and trunk. For nine days there were repeated episodes of headache and vomiting and increased drowsiness.

Examination.—On admission the boy appeared acutely ill, with cyanotic lips and skin, moderate exophthalmos and typical clubbing of the fingers. There were a pronounced bulging of the pulmonary conus, an apical thrill during systole and a loud rough murmur over the entire precordium, most marked over the apex (tetralogy of Fallot). The blood pressure was 100 systolic and 70 diastolic, the temperature 99 F., the pulse rate 75 and the respiratory rate 22.

The positive neurologic findings were bilateral papilledema, more advanced on the right, ptosis of the right eyelid, hypesthesia of the left cornea, weakness of the left side of the face, left hemiparesis, more marked in the arm, absence of abdominal reflexes on the left side, and more active deep reflexes on the left side.

Laboratory Data: The urine was normal. The blood count revealed: hemoglobin, 91 per cent, erythrocytes, 8,750,000 per cubic millimeter, and leukocytes, 5,200 per cubic millimeter, with 73 per cent polymorphonuclear cells and 24 per cent lymphocytes. The blood sugar value was 106 mg., the creatinine content 1.4 mg., and the urea nitrogen content 10.8 mg. per hundred cubic centimeters. Roentgen examination of the chest showed a broadened cardiac shadow of the left ventricular region, suggesting hypertrophy. Wassermann and Kahn tests of the blood

gave negative reactions. The electrocardiogram revealed dominant sinus rhythm, right axis deviation and auricular hypertrophy. The sedimentation rate was 8 mm. in one hour. Examination of the spinal fluid revealed a pressure of 480 mm.; no cells; a sugar content of 78 mg.; 729 mg. of chlorides per hundred cubic centimeters, and a total protein value of 33 mg. per hundred cubic centimeters. No organisms were revealed by smear or culture.

Course.—During the first week of observation the headaches subsided, vomiting became less frequent and drowsiness grew less marked. At times pain over the right eye became severe. The papilledema gradually increased. There was no evidence of an enlarged spleen, of petechiae or of positive results of blood culture. On the tenth day after admission the temperature was 100.6 F. and the pulse rate 55, and the patient suddenly lost consciousness for five minutes. Ankle clonus and the Babinski sign on the left side were now present, but in addition the right arm became spastic and there was also a positive Babinski sign on the right.

Operation.—Operation was performed on Aug. 3, 1935, with the region under local procaine hydrochloride anesthesia, a trephination being done over the right parietal area. The exposed dura appeared normal and, surprisingly, pulsated

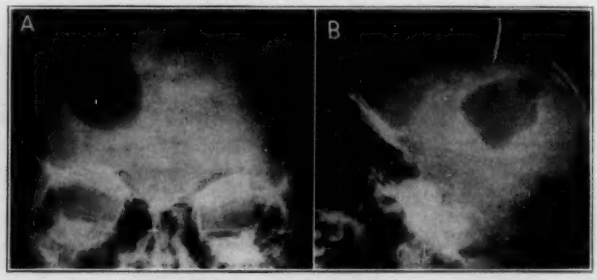

Fig. 1.—*A*, aerogram showing position of the abscess cavity in the right parietal lobe (case 1); *B*, lateral view of the abscess cavity (case 1).

freely. A ventricle needle was inserted, and at a depth of 5 cm. pus was obtained. Sixty cubic centimeters of pus was aspirated. A smear of the pus showed gram-negative bacilli and gram-negative diplococci. Cultures for aerobic and anaerobic organisms showed no growth. The day following the operation the patient was conscious. The right pupil was larger than the left. There was palsy of the left external rectus muscle; the neck was stiff, and there was a bilateral Kernig sign. The temperature was 101 F. and the pulse rate 78. During the next two weeks the patient showed some improvement; the neck was less rigid, and there was some return of power in the left arm and leg. At times he vomited and complained of pain in the right eye. The temperature remained below 100 F. for a week. However, the papilledema did not subside. Then the frontal headache and the pain in the right eye returned, nausea and vomiting increased and the patient complained of gustatory and olfactory hallucinations.

On Aug. 19, 1935 at 2:30 a. m., after a generalized convulsion, he lost consciousness and presented the picture of decerebrate rigidity. Aspiration through the trephine opening yielded 50 cc. of pus. He regained consciousness shortly thereafter; the headaches disappeared, and he remained in a satisfactory state for

the next three days, when the headaches recurred, vomiting followed and the left hemiparesis became more pronounced. Aspiration through the trephine opening was repeated and 45 cc. of pus removed. At this time 25 cc. of air was injected. Roentgen examination of the skull (fig. 1 *A* and *B*) showed a well rounded air pocket about 4 cm. in diameter in the right parietal region.

Although the patient improved for two days after this procedure, the headaches and vomiting recurred and he appeared extremely ill. A more radical operation was decided on. On Aug. 24, 1935 the wound and bone defect were enlarged, the dura coagulated at the bone margins, the brain incised and a Mosher drain inserted into the abscess cavity. For one week after this operation there was remarkable improvement, but then the headaches returned, the papilledema progressed and a bilateral Kernig sign and a Babinski sign on the left again became evident. Vomiting continued, the temperature rose to 101 F. and the pulse rate to 120, and the paresis became more marked. The spinal fluid was cloudy and showed 4,000 leukocytes per cubic millimeter, with 84 per cent polymorphonuclears and 14 per cent lymphocytes. Two cultures of the blood yielded no growth. Repeated studies of the spinal fluid showed increase in pressure and pleocytosis, the cells being chiefly mononuclear, but no organisms were revealed by smear or culture. Clinically the patient presented the picture of meningitis with spreading encephalitis. He died fifty days after admission to the hospital. Necropsy was refused.

Case 2.—A school girl 11½ years of age was admitted to the Mount Sinai Hospital on March 31, 1939. At birth the child was recognized as a "blue baby" and was known to have congenital heart disease. During early childhood she had measles, chickenpox and whooping cough.

Three months before admission, for three weeks, she had cough and fever which were diagnosed as bronchitis. On March 27, 1939, four days before admission, she began to complain of headache in the right supraorbital region. This was the only symptom for three days, when she suddenly had typical jacksonian clonic convulsions of the entire left leg. There was no aura or loss of consciousness; the seizure lasted about one minute and was followed by weakness of the left leg. Several hours after this attack she had a second one, identical with the first. On the morning before admission to the hospital, weakness of the left arm also became apparent, and during the afternoon she had a third convulsion.

Examination.—On admission, examination showed a tall thin girl, with blue lips and long, clubbed, cyanotic finger tips with curved nails. She complained of headache. The temperature was 102 F. and the pulse rate 96 and the respiratory rate 22 per minute. Examination of the heart showed congenital heart disease with the "tetralogy of Fallot." There was a systolic thrill over the third left interspace at the sternal margin. There was also a loud harsh systolic murmur, which was transmitted from this region over the entire precordium. The first sound at the apex was snapping, and the aortic second sound was louder than the pulmonic second sound. The systolic blood pressure was 100 and the diastolic 60. The electrocardiogram showed right axis deviation and high voltage, which are seen in patients with congenital heart disease. Roentgen films of the chest revealed moderate enlargement of the heart to the right, a widened arch and diminution in the size of the root of the left pulmonary artery. Roentgenograms of the skull showed the pineal shadow displaced to the left.

The neurologic findings were a weakness of the left side of the face, some spasticity of the left leg, positive Babinski and Chaddock signs on the left side and a transient ankle clonus on the left side.

Laboratory Data: The urine was normal. The hemoglobin content of the blood was 110 per cent, with 6,100,000 red blood cells per cubic millimeter. The leukocytes numbered 15,000 per cubic millimeter, 66 per cent being polymorphonuclear cells and 28 per cent lymphocytes. The Wassermann reaction of the blood was negative. Blood culture showed no growth. The spinal fluid was under initial pressure; it gave a 4 plus reaction to the Pandy test and had 3 lymphocytes per cubic millimeter.

During the first four days after admission the patient continued to complain of frontal headache. There were a few nystagmoid jerks on right lateral gaze. The temperature ranged between 98 and 101 F. and the pulse rate from 54 to 60. The right fundus became hyperemic. The left cornea became less sensitive and the neck slightly stiff. The abdominal reflexes could no longer be obtained. The patient became drowsy. The spinal fluid showed an initial pressure of 118 mm.; the reaction to the Pandy test was 2 plus, and there were 25 lymphocytes per cubic millimeter. Thirty cubic centimeters of air was injected through the lumbar route but none appeared in either ventricle; there was some air over the left cortex

Fig. 2.—*A*, air in the abscess cavity (case 2); *B*, lateral view of the abscess cavity (case 2).

and in the basilar cistern. The increasing drowsiness, the bradycardia and the advancing papilledema pointed to an expanding intracranial lesion.

On April 8, with the area under local procaine hydrochloride anesthesia, a trephine opening was made in the right frontal region, about 1 inch (2.5 cm.) from the midline. The exposed dura did not pulsate. At a depth of 4 cm. a ventricle needle encountered brownish gray purulent material. Seventy cubic centimeters of foul-smelling matter was removed by aspiration and the wound closed without drainage. The pus on smear showed gram-positive cocci in pairs and in chains. Culture showed a growth of Streptococcus viridans A. Sulfapyridine therapy was started.

After operation the patient became more alert and was no longer troubled with headache, but she complained of extreme nausea, which undoubtedly was due to the sulfapyridine. Within the next four days there was remarkable improvement. She showed more motion in the left leg and some movements of the fingers of the left hand, and she had only occasional headache. One week after the operation she suddenly cried out and became stuporous. Lumbar puncture was again per-

formed. The spinal fluid was under low pressure, 80 mm. It was clear and contained 9 lymphocytes. There was a 3 plus reaction to the Pandy test and the sugar content was 70 mg. per hundred cubic centimeters. The patient regained consciousness after the lumbar puncture. Aspiration through the previous trephine opening yielded 30 cc. of much thicker yellow pus. The sulfanilamide content of the pus was 8.3 mg. per hundred cubic centimeters, as compared with 9.5 mg. in the blood.

The following day the patient was again drowsy. Forty cubic centimeters of pus was aspirated, this time through the previous trephine opening and 25 cc. of air injected. Roentgenograms of the skull (fig. 2 *A* and *B*) showed a cavity 1 by 1½ inches (2.5 by 3.8 cm.) in the right parietal region.

On April 18 a second operation was performed, with the patient under nitrogen monoxide–oxygen anesthesia. The previous wound was reopened, the bone defect enlarged to the size of a quarter, the dura sealed off with a coagulating current and the brain incised. At a depth of 3 cm. a firm capsule was seen. A rubber tube drain was inserted. There was an escape of about 30 to 40 cc. of thick pus.

Although the patient became more alert, the headaches continued, the fever took on a septic character, the neck became stiff and the left hemiparesis became worse. She became stuporous, and died forty-three days after the onset of symptoms and thirty days after operation.

SUMMARY

The 2 cases of cerebral abscess are reported, first, because of the rarity of the condition and, second, because early recognition may possibly lead to successful surgical relief. Altogether, 12 cases have been reported in the literature, and the 2 additional ones bring the total to date up to 14. In only 3, including our own 2, was the condition diagnosed during life and therefore treated surgically; in the rest the anomaly was not even suspected. As a rule a diagnosis of embolism or thrombosis is made. The rapidity with which the abscess generally forms justifies in some measure such a diagnosis. But the presence of fever, of leukocytosis, possibly of slow pulse and of early fundus changes should draw attention to the presence of an expanding intracranial lesion, more particularly an abscess. In cases in which the diagnosis is doubtful, pneumoencephalographic examination may be indicated. The important point to bear in mind is that abscess of the brain, though rare, can occur in patients with congenital heart disease, even though a primary focus of infection may not be detected. In any event, early recognition as well as familiarity with the complication and with the underlying pathologic changes may lead to more successful surgical intervention.

PNEUMOCOCCIC PNEUMONIA

ANALYSIS OF THE RECORDS OF 1,469 PATIENTS TREATED IN THE LOS ANGELES COUNTY HOSPITAL FROM 1934 THROUGH 1938

I. CHARACTER OF PNEUMONIA CAUSED BY THE VARIOUS TYPES OF PNEUMOCOCCI; COMPLICATIONS; OUTCOME OF PNEUMONIA IN THE PRESENCE OF CERTAIN VARIATIONS IN THE PATIENT AND IN THE COURSE OF THE DISEASE

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Pneumococcic pneumonia is highly variable in causation, pathologic aspects, course and outcome. A clear knowledge of the range and significance of its variations is requisite to an adequate concept of the disease, to intelligent management of the patient and to any interpretation of the results of treatment. In this and the two succeeding papers are published the results of a study of the records of 1,469 patients with pneumococcic pneumonia. This paper is concerned with the development, course and outcome of the disease caused by the various types of pneumococci, with the complications of pneumonia and with alterations in the outcome attending certain variations in the patient and in the course of the disease. The second paper will deal with the character of the disease in the presence of associated or concomitant conditions and the third with the results of serum therapy.

MATERIAL AND METHODS

During the five year period from 1934 through 1938, about 10,000 patients with certain or probable "primary" or "secondary" pneumonia were treated in the Los Angeles County Hospital. Pneumococci were recovered in approximately 1,600 of the cases, the cause not being investigated in most of the others. By

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From the Department of Medicine, School of Medicine, University of Southern California, and from the Los Angeles County Hospital.

some of the workers detailed abstracts were prepared of the entire clinical, nursing and laboratory record of each patient from whom pneumococci were recovered. One of the workers checked the abstracts with the original records, prepared the data for tabulation and supervised the analysis. When there was disagreement in clinical notations, the reviewer weighed the data in favor of the more experienced observer. When clinical and roentgen evidence were in persistent disagreement, the clinical evidence was accepted; most frequently the discrepancy was temporary and did not involve the reviewer's discretion. In some cases in which pneumococci were recovered the presence of pneumonia was ruled out, and in others two or more types were recovered during a single illness; the records of such cases were discarded. The patients in the remaining cases, whose records form the basis of these papers, numbered 1,469, and all of them had clear evidence of pneumonia due to a single type of pneumococcus. It must be emphasized that the study was planned in the latter part of 1938 and has therefore been conducted on completed hospital records which were prepared without particular attention to the possibility of a survey; they were not systematized as to collection or recording of information, and experimental methods were not used.

Until the latter part of 1936, types I, II and III were determined by precipitin methods, "group IV" of our series including all pneumococci recovered but not typed. Since then the Neufeld method has been used to determine all of the Cooper types, and the term "group IV" was abandoned. Direct examinations of sputum were used rather than the method of mouse passage. Although cultures of the body fluids were not routinely made,[1] they were helpful in establishing or confirming the cause. No review of physical findings is published in these papers, but only the final diagnosis. The term "atypical" is used to indicate disease with distinctly atypical history, findings and course, and "lobar" to indicate lesions not definitely atypical. (When all clinical evidence pointed to one or the other diagnosis, that diagnosis was retained in this report even if contradicted by observations at autopsy; only if there was some doubt ante mortem did the autopsy observations influence the diagnosis as reported in these papers.) All patients who died are included under the heading "death" whether they died from pneumonia with or without complications, from complication persisting after cure of the pneumonia or from an accident during pneumonia or its sequelae. The term "complication" includes all complications, except bacteremia, referable to the local pathologic process or to dissemination of the pneumococci (small pleural exudates discoverable only by roentgen examination or autopsy were disregarded). Survival without complication is called "optimum outcome," publication of that rate being necessary for the calculation of the overlap between the "mortality" and the "complication" rate; this overlap occurs because patients who die with complications are recorded under "death" and also under "complication." Simple statement of mortality and complication rates is ambiguous: If 50 per cent died and 50 per cent had complications, it is possible, depending on the degree of overlap, that all the patients had an unfortunate outcome or that half survived without complication. The per cent of all patients who died with complications is obtained by subtracting 100 from the sum of the three rates.

The data are summarized in tables, the written text being reserved for those aspects which appeared most interesting. The literature on these subjects is so voluminous that adequate references cannot be cited with brevity.

1. Laboratory facilities during the time covered by this report did not permit routine blood cultures.

RESULTS

The incidence of the types each year and for the five year period, as well as the annual incidence of pneumococcic pneumonia, are recorded in table 1. The apparent increase in pneumococcic pneumonia probably reflects an increase in effort to determine type rather than a true increase in incidence of the disease. Types I, II and III were responsible for less than half the infections, occurring in 42 per cent of the 1,469 patients—an incidence considerably less than that usually reported for the north Atlantic seaboard. The order of frequency of the Cooper types could be determined only for 1937 and 1938, the ten most frequent types being types I, VII, III, VIII, II, V, IV, IX, VI and XIV.

TABLE 1.—*Distribution (per Cent) of Types for Each Year and for Five Years; Annual Incidence and Percentage of Five Year Total*

Type	Per Cent Each Year					Per Cent 5 Years	Total Cases
	1934	1935	1936	1937	1938		
I	12	10	22	30	21	22	320
II	19	4	10	7	5	7	104
III	13	10	12	13	14	13	190
IV	..	..	1	5	6	4	55
V	..	..	2	6	6	4	59
VI	..	..	1	2	3	2	28
VII	..	..	10	18	14	12	172
VIII	..	..	3	7	7	5	70
IX	..	..	0	4	4	2	36
XIV	..	..	1	1	2	1	15
Others *	..	..	2	8	17	8	122
Group IV	55	75	39	..	..	20	298
Annual incidence number	67	192	301	388	521	..	1,469
Per cent of 5 year total	5	13	20	26	36	100	

* The term "others" indicates Cooper types X to XIII and XV to XXXII, each of which was represented by inadequate numbers of patients to warrant separate presentation (table 16).

The prevalence of pneumococci, especially of the higher types, in the respiratory passages of normal persons introduces a question of the reliability of typing by examination of sputum. The problem is not so much the identification of the pneumococci as it is the relation of the recovered organisms to the pneumonia. The more efficient the method of recovering the organisms, the more probable is the recovery of organisms incidentally present in the nose and throat; methods such as that of mouse passage, used to determine carriers in the normal population, would also find them among patients with pneumonia. Direct examination of the sputum, however, requires large numbers of organisms in the sputum, for otherwise the chances of seeing them are slight. The more crude the method, the more the sputum must be loaded with organisms to give positive results. The more common false negative results become, the more reliable are the positive results likely to be (ruling out laboratory errors). We reviewed the results of the examina-

tion of 249 samples of sputum taken from 157 patients (consecutively admitted to one ward) in whom the presence of pneumonia due to a definite type of pneumococcus was established by the finding of the organisms in several samples of sputum or by culture of body fluids. In only 73 per cent of the samples were pneumococci found. We assume that the remaining 27 per cent of the reactions represent false negative results. Laboratory errors appeared, so far as we could determine, in less than 1 per cent of all examinations. It is probable, then, that the type of pneumococcus recovered from the sputum was the etiologic agent of the pneumonia.

TABLE 2.—*Outcome in Cases of Pneumonia, Incidence of Concomitant Conditions, and Outcome and Incidence of Serum Therapy with Such Conditions Present or Absent*

Type	Outcome (%)			Incidence (%) of Concomitant Conditions	Concomitant Conditions (%)					
					Present			Absent		
	Optimum*	Death	Complication		Death	Complication	Serum Therapy†	Death	Complication	Serum Therapy†
I	66	17	23	38	23	23	80	14	24	77
II	58	28	26	34	34	20	60	25	29	62
III	58	34	18	57	39	19	24	28	16	12
IV	67	22	15	62	26	3	26	14	33	24
V	61	25	22	59	31	26	74	17	17	57
VI	67	33	11	63	33	17	17	33	0	33
VII	64	24	16	49	28	15	72	20	16	68
VIII	67	20	24	67	28	23	38	4	26	26
IX	69	14	17	67	17	13	0	8	25	17
XIV	60	20	20	47	43	29	29	0	13	17
Others	75	17	11	71	20	7	6	8	19	11
Group IV	65	21	18	47	26	14	0	17	21	0
All types	65	23	19	51	28	17	36	17	21	41

* Survival without complication.
† Treatment with type-specific serum.

Data are presented in tables 2 through 12 concerning the outcome, history, diagnosis, laboratory findings and febrile course of the pneumonias associated with each type. Some of the findings for the four Cooper types represented by 100 or more patients (I, II, III and VII) are outlined in the following paragraphs.

Type I pneumococci were recovered in material from 320 patients, of whom 66 per cent survived without complications (optimum outcome), 23 per cent had complications and 17 per cent died. The total of the three rates is 106 per cent, indicating that 6 per cent of the patients died with complications. Concomitant conditions were recognized in only one third of the patients, many of these disorders being respiratory and very few cardiac. The mortality rate was greater in the presence of known concomitant conditions than in their presumed

absence, as was true of almost every type. Four fifths of all patients with pneumonia due to pneumococci of type I received antipneumococcus serum.[2]

Of the 75 patients in whom complication developed, 48 per cent had empyema and 20 per cent had pleural effusions,[3] while 19 per cent had otitis media. The heart and pericardium were rarely involved (table 3).

The seasonal incidence of type I pneumonia conformed closely to that usually described for more rigorous climates. Nearly one-half the patients were between 20 and 40 years of age, while few were over 60.

TABLE 3.—*Relative Frequency (per Cent) of Various Complications Among All Patients with Complications* *

	Percentage of Patients with Named Complication Among All Those with Complications										
Type	Empyema	Pleural Effusion	Otitis Media	Meningitis	Pulmonary Abscess	Endocarditis	Pericarditis	Thrombophlebitis	Peripheral Embolism	Pericardial Effusion	All Other Complications
I	48	20	19	1	2	2	0	2	1	0	4
II	34	29	3	9	0	11	9	3	3	0	0
III	22	35	16	8	3	0	8	0	3	3	3
IV	33	22	11	11	11	11	0	0	0	0	0
V	53	6	12	6	6	12	0	0	6	0	0
VI	0	100	0	0	0	0	0	0	0	0	0
VII	10	48	10	3	3	3	0	0	7	0	14
VIII	20	24	20	12	8	0	0	4	0	4	8
IX	50	33	17	0	0	0	0	0	0	0	0
XIV	0	67	0	0	33	0	0	0	0	0	0
Others	31	31	8	8	8	8	0	0	8	0	0
Group IV	30	31	5	6	5	3	5	8	2	2	5
All types	33	28	12	5	4	4	3	3	2	1	4

* Patients with more than one complication are listed once under each.

Almost all were Caucasian or Mexican, and two thirds of the patients were male (table 4).

In about half the histories of patients with pneumonia of type I there was no mention of complaints preceding the onset of pneumonia, while in 43 per cent there were complaints referable to the respiratory tract. The latter rate is probably an understatement of the true incidence. Thirty per cent of the patients were admitted during the first two days following the onset, 60 per cent during the first four days and 81 per cent

2. Evaluation of the effects of such therapy is readily seen to be difficult and to require separate study when it is learned that the treatment itself varied greatly and that there were no controls, serum being given to almost all patients who might be aided by it.

3. Since it is felt that if serial roentgen studies were routinely made, minimal amounts of pleural fluid would be discovered in almost all patients, "pleural effusion" has been termed a "complication" only when it was voluminous enough to attract clinical attention.

during the first six days. In patients without known concomitant conditions, the major symptoms of pneumonia (in the order of frequency) were fever, painful respiration, chill, cough (excluding patients with

TABLE 4.—*Distribution (per Cent) of Patients According to Season, Age, Race and Sex* **

Type	Season				Age (Yr.)				Race				Sex, (% Male)
	May to Sept.	Oct. and Nov.	Dec. to Feb.	March and April	0 to 19	20 to 39	40 to 59	60 and Over	Caucasian†	Mexican	Negro	Miscellaneous‡	
I	22	14	42	23	18	46	29	7	76	18	6	1	67
II	22	13	47	19	19	45	34	5	67	27	7	1	74
III	19	11	54	17	7	29	30	35	74	16	7	2	64
IV	15	21	56	7	13	40	34	13	71	7	20	2	60
V	15	8	55	22	15	44	25	15	73	22	5	0	70
VI	33	21	32	14	8	53	29	11	82	11	7	0	61
VII	15	12	48	24	15	36	36	12	67	23	9	1	68
VIII	17	21	47	15	4	33	37	26	79	11	7	3	61
IX	18	22	45	16	6	47	25	22	75	11	14	0	72
XIV	21	26	27	26	26	20	26	27	80	7	7	7	60
Others	25	16	41	17	12	33	33	23	76	13	10	1	66
Group IV	18	9	47	26	11	49	32	8	70	19	10	1	61
All types	19	13	47	21	13	41	31	15	73	18	8	1	65

* Typing of infants and children was less frequently attempted than that of adults.
† Excluding Mexicans.
‡ All other races (mostly far Eastern).

TABLE 5.—*Analysis of Histories of All Patients, Showing Symptoms Preceding Onset of Pneumonia and Number of Days From Onset* * *to Admission*

Type	Complaints Preceding Onset of Pneumonia, Distribution (%)					Number of Days from Onset to Admission Distribution (%)					
	None Recorded	Respiratory Infection †	Malaise ‡	Gastrointestinal	Others	1, 2	3, 4	5, 6	7, 8	9 and Over	?
I	48	43	4	2	3	30	30	21	12	6	1
II	46	47	2	1	6	29	34	17	10	8	2
III	39	50	2	1	7	31	26	16	14	9	4
IV	45	35	2	1	15	36	34	16	7	4	2
V	39	47	2	1	12	31	27	28	14	2	0
VI	25	39	7	7	21	43	25	18	11	4	0
VII	50	40	3	2	5	26	30	17	16	10	0
VIII	40	49	0	1	10	30	30	16	12	7	3
IX	31	42	3	0	25	45	20	12	14	11	0
XIV	27	60	0	0	13	33	40	7	0	13	7
Others	32	41	1	4	21	45	22	11	6	15	2
Group IV	43	47	6	1	5	23	33	19	14	7	4
All types	43	45	3	1	8	30	30	18	12	7	2

* "Onset" is understood here as the first appearance of pain on respiration, fever, chill, bloody sputum, dyspnea, prostration or coma, or, in the absence of those symptoms, a sudden change for the worse in an infection of the respiratory tract.
† Usually in the upper expiratory tract, with or without complaints referable to other systems.
‡ Vague symptoms not referable to any particular system.

cough prior to the onset), bloody sputum and dyspnea. At least five of these symptoms were present in 22 per cent of the patients, at least four in 57 per cent and at least three in 82 per cent, while only 4 per cent of the patients had but one symptom. The usual explosiveness of the

syndrome is indicated by the fact that less than one day elapsed between the appearance of the first and the last of these symptoms in 72 per cent of the patients—only 17 per cent, without concomitant conditions, being admitted within one day of the onset (tables 5 and 6).

Definitely atypical pulmonary involvement was rare among patients with type I pneumonias, and nearly one third of the more typically lobar lesions involved more than one lobe. Although pneumococci were observed in the blood of 9 per cent of the 90 patients for whom cultures were made, that figure cannot be accepted as indicating the incidence of

TABLE 6.—*Analysis of Histories of Patients Without Known Concomitant Conditions, Showing Incidence of Major Symptoms of Pneumonia, and Distribution of Patients According to Number of These Symptoms per Patient and to Number of Days Between Onset of First and Last of These Symptoms*

	Major Symptoms (%)						Distribution (%) of Patients: According to No. of These Symptoms			According to No. of Days Between First and Last Symptom			
Type	Pain on Respiration	Fever	Chill*	Cough†	Bloody Sputum‡	Dyspnea	0 to 2	3 or 4	5 or 6	0 to 1	2 to 3	4 to 6	7 and Over
I	81	85	70	59	40	25	18	60	22	72	16	10	2
II	83	75	61	67	51	22	20	54	26	72	13	9	6
III	82	68	63	76	46	15	24	47	28	79	12	7	1
IV	86	81	67	67	48	33	19	43	38	86	10	0	5
V	75	67	67	42	42	33	37	33	29	67	17	17	0
VI	90	80	90	50	50	20	0	80	20	60	20	10	10
VII	81	67	65	67	52	25	18	56	26	61	19	18	2
VIII	83	91	78	87	35	22	26	43	30	78	22	0	0
IX	75	88	50	56	25	8	25	67	8	75	25	0	0
XIV	100	75	63	63	38	0	25	63	13	75	13	0	13
Others	77	86	63	60	46	34	20	46	34	63	23	6	9
Group IV	82	73	64	63	44	23	19	61	20	76	15	4	6
All types	82	77	66	63	44	23	20	56	24	72	16	8	4

* Rigor or severe chilly sensations.
† Only patients whose cough developed at or after the onset of pneumonia are included.
‡ Bloody, rusty, brown or orange sputum (the latter terms are often used by Mexicans).

bacteremia, for cultures were made only under special circumstances. The maximum total leukocyte count recorded, made during the acute pneumonia, was within normal limits for 11 per cent and between 10,000 and 30,000 for 77 per cent of the patients studied (table 7).

The highest temperature[4] observed during the first few hours of hospitalization exceeded 103.5 F. for 41 per cent of the patients with

4. There are numerous evidences of the progress of the disease, but the only signs that are readily measured are the temperature, the pulse rate and the respiratory rate. The respiratory rate is not, according to our experience, measured with sufficient care to be reliable (the nurses usually being too pressed for time). The pulse rate is usually less labile than the temperature, tending to be elevated for some little time after the fever is abolished. The temperature has therefore

(Footnote continued on next page)

type I pneumonia but was less than 101.5 F. for 13 per cent. There was a generally flat, or horizontal, temperature curve for only one fourth of the patients, while for 63 per cent the temperature curve progressively tended to fall. Fluctuations of the temperature were insignificant for 19 per cent, moderate (usually from 1 to 3 degrees) for 74 per cent and marked for only 4 per cent of the patients. Some further indication of the course is found in the fact that 70 per cent of the patients received oxygen, which is routinely given in the presence, to a moderately alarming degree, of hyperpnea, cyanosis, tachycardia or delirium (table 8).

TABLE 7.—*Distribution (per Cent) of Patients According to Pulmonary Involvement, to Incidence of Positive Blood Cultures Among Patients from Whom Cultures Were Taken, and to Maximum Recorded Total Leukocyte Count (in Thousands)*

	Pulmonary Involvement								Blood Culture		Maximum Recorded Total Leukocyte Count (in Thousands)†					
	Lobar*				Atypical											
	No. of Lobes					Extent										
Type	1	2	3+	Total	Total	Minimal	Moderate	Extensive	No. of Patients	Percentage Positive	No. of Patients	1 to 4	5 to 9	10 to 19	20 to 29	30 and Over
I.....	64	19	12	95	3	1	1	1	85	9	199	1	11	50	27	12
II.....	54	23	17	94	6	2	1	3	17	29	78	3	14	52	27	5
III.....	44	15	7	66	33	10	14	9	26	12	115	2	15	42	26	17
IV.....	69	5	7	81	19	2	13	4	11	10	36	3	17	48	28	6
V.....	56	19	10	85	15	3	7	5	9	22	38	0	3	66	16	16
VI.....	36	18	7	61	40	11	25	4	4	0	17	0	29	47	24	0
VII.....	60	18	11	89	11	2	6	3	26	15	107	1	14	50	23	10
VIII.....	59	13	10	82	19	9	4	6	16	25	49	2	6	60	22	10
IX.....	67	11	3	81	20	3	14	3	6	0	25	0	7	56	23	15
XIV.....	53	20	0	73	27	7	13	7	5	40	11	0	0	36	45	18
Others...	46	11	2	59	40	9	24	7	24	4	63	0	25	41	22	11
Group IV	56	18	10	84	15	5	8	2	13	23	199	1	13	47	30	10
All types	56	17	10	83	17	5	8	4	242	14	937	1	13	49	26	11

* "Lobar" includes all involvement not definitely atypical and is chiefly a clinical diagnosis.
† Figures are for the patients for whom leukocyte counts were made during the acute stage of the illness.

In 22 per cent of the cases of type I pneumonia the first normal temperature was observed during the first four days of illness, in 45 per cent between the fifth and the eighth day and in 23 per cent on or after the ninth (only 6 per cent of the patients were admitted on or after the ninth day), there being no defervescence in 11 per cent. Among patients

come to be of great significance, and special attention was devoted to the defervescence and to the recurrence of fever in these patients. Rigid criteria were adopted, the term "normal" indicating a temperature of 99 F. or less and "crisis" indicating a fall of temperature during no more than twenty-four hours. The temperature was considered only during the interval in which the course was uncomplicated; hence the statement that in a patient with complication there was "no defervescence" means only that there was none prior to the recognition of the complication.

who died without complication, crisis [5] was twice as common as lysis, while crisis and lysis occurred with about equal frequency among all other patients. A defervescence was observed in all of the patients who survived without complications and in 96 per cent of those who survived and had complications, but in only 54 per cent of those with complications who died and in 30 per cent of those without complications who died (table 9).

TABLE 8.—*Distribution (per Cent) of Patients According to Fever* and Incidence of Treatment with Sulfanilamide, Antipneumococcus Serum or Oxygen*

	Temperature (F.) on Admission					General Appearance of Temperature Chart During Uncomplicated Febrile Course						Incidence (%) of Treatment		
						Trend			Variation †					
Type	To 100	101	102	103	104 and Over	Plateau	Better	Worse	Insignificant	Moderate	Marked	Sulfanilamide	Serum	Oxygen ‡
I.....	5	8	18	28	41	25	63	9	19	74	4	9	78	70
II.....	9	8	17	40	26	35	55	11	14	81	6	11	62	65
III.....	15	8	26	29	21	34	54	13	12	85	4	17	19	63
IV.....	7	11	24	33	25	33	56	11	16	78	6	16	25	58
V.....	8	14	19	32	27	30	51	17	21	69	8	8	66	63
VI.....	18	14	25	11	32	32	53	14	7	92	0	29	21	54
VII.....	9	9	23	31	28	25	59	15	16	79	4	14	79	67
VIII.....	13	16	24	30	17	26	61	13	19	77	4	26	34	54
IX.....	17	14	28	25	17	22	64	14	14	83	3	33	6	72
XIV.....	7	13	20	0	60	40	53	7	0	100	0	13	33	67
Others.....	10	16	29	25	21	29	62	8	7	87	5	20	7	61
Group IV.....	8	13	26	30	22	30	59	11	16	77	7	0	0	58
All types.....	9	11	23	29	27	29	59	11	15	80	5	12	39	63

* The distribution according to fever is based on (1) maximum temperature recorded during the first few hours after admission and (2) general appearance of the temperature chart before cure, death or recognition of complications.

† The significance of terms describing trend, or general slope, is as follows: "plateau" means flat; "better," falling, and "worse," rising. Fluctuations designated as "insignificant" were usually less than 1 degree; as "moderate," usually from 1 to 3 degrees, and as "marked," usually more than 3 degrees.

‡ Oxygen was routinely given for dyspnea, cyanosis, tachycardia or delirium.

Of the patients who had a defervescence, a recurrence of fever was noted in 64 per cent of those surviving and having no complications, 80 per cent of the survivors with complications, 76 per cent of those who had complications and died and 70 per cent of those without complications who died (table 10). From these data may be computed the percentage of patients who had a defervescence with no subsequent fever, the results being shown in table 13 for types I, II, III and VII. Type I pneumonia was terminated within the first four days in 15 per cent of

5. "Crisis," as has already been mentioned, was strictly defined as a fall of temperature from peak to less than 99 F. in less than twenty-four hours, regardless of the possible cause of the defervescence.

the patients who survived without complications and in 6 per cent of those who died without complications, no complications having been recognized during that time. By the tenth day, however, 71 per cent

TABLE 9.—*Distribution (per Cent) of Patients with Respect to Days Between Onset of Pneumonia and First Normal Temperature and to Outcome According to Manner of First Defervescence* *

	Number of Days from Onset to First Normal Temperature †							Outcome According to Manner of First Defervescence								
								Not Complicated				Complicated				
								Well		Dead		Well			Dead	
Type	1 or 2	3 or 4	5 or 6	7 or 8	9 or 10	11 and Over	? or No Defervescence	Crisis ‡	Lysis §	Crisis	Lysis	No Defervescence	Crisis	Lysis	No Defervescence	Crisis	Lysis	No Defervescence
I.....	5	17	24	21	11	12	11	55	45	21	9	70	45	51	4	27	27	46
II.....	2	18	22	22	8	13	15	55	45	24	12	64	40	60	0	35	25	42
III.....	9	9	20	18	11	14	20	50	50	30	20	50	47	47	6	32	21	47
IV.....	7	19	26	16	8	9	16	46	54	20	0	80	33	67	0	50	50	0
V.....	3	15	21	24	10	14	14	64	36	40	20	40	38	50	13	20	20	60
VI.....	18	18	8	22	11	7	18	56	44	29	14	57	0	100	0	0	50	50
VII.....	3	14	23	20	18	11	12	54	46	37	11	53	43	57	0	33	17	50
VIII.....	13	17	10	21	11	14	13	57	40	0	50	50	44	56	0	25	25	50
IX.....	6	14	17	25	14	14	11	52	48	20	40	40	33	33	33	..	..	..
XIV.....	7	7	33	13	0	27	13	56	44	33	0	67	67	33	0	..	..	..
Others.....	9	17	22	17	6	16	11	51	49	24	18	59	33	56	11	25	25	50
Group IV...	5	7	19	21	12	21	16	39	60	22	20	50	32	68	0	33	17	50
All types....	6	13	21	20	11	15	14	51	49	26	16	58	40	56	4	29	24	47

* All data concerning the temperature refer exclusively to the interval in which no complication had appeared.
† By "normal" is meant 99.0 F. or less.
‡ Less than twenty-four hours from peak to first normal temperature.
§ More than twenty-four hours from peak to first normal temperature.

TABLE 10.—*Incidence of Recurrence of Fever* * in Patients Who Had a Defervescence (Tabulated According to Outcome)*

	Not Complicated		Complicated	
Type	Well	Dead	Well	Dead
I.....	64	70	80	76
II.....	72	100	75	86
III.....	76	87	86	90
IV.....	81	100	83	100
V.....	67	100	43	100
VI.....	89	100	100	0
VII.....	67	94	76	100
VIII.....	60	67	78	100
IX.....	60	100	100	...
XIV.....	78	100	67	...
Others.....	73	86	63	100
Group IV.....	60	100	66	83
All types.....	68	93	75	87

* "Fever" means a temperature of 99.0 F. or over, and only the temperature during the uncomplicated interval is considered.

of the patients surviving without complications were cured, 60 per cent of those having no complications and dying had died and 43 per cent of the complications had been recognized (table 11).

The duration of hospitalization for type I pneumonia and its sequelae was less than two weeks in the case of 67 per cent of patients who survived and had no complications and in 17 per cent of those with complications who survived. Of the patients who died and had no complications about 80 per cent died within the first five days of hospitalization and 18 per cent within the first day. Of those with complications who died, 54 per cent died within the first week and 27 per cent within the first two days of hospitalization (table 12).

TABLE 11.—*Distribution (per Cent) of Patients by Outcome According to Duration of Uncomplicated Febrile State* *

	Not Complicated												Complicated					
	Well						Dead						Well or Dead					
Type	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?
I.....	15	28	28	17	12	0	6	36	18	18	12	9	0	11	32	23	31	3
II.....	8	32	25	20	13	2	0	24	24	18	35	0	11	15	23	21	26	4
III.....	10	26	24	24	15	2	4	39	31	18	7	2	3	12	33	21	26	6
IV.....	11	35	27	8	19	0	20	60	10	0	0	10	0	38	0	26	37	0
V.....	19	31	25	11	14	0	0	30	20	20	30	0	8	24	31	8	31	0
VI.....	11	28	39	6	17	0	0	57	14	14	14	0	0	33	33	33	0	0
VII.....	13	25	28	19	14	0	6	23	46	18	9	0	0	11	37	26	26	0
VIII.....	17	23	33	12	13	2	17	17	67	0	0	0	0	6	24	24	41	6
IX.....	8	12	40	8	32	0	0	60	0	20	20	0	0	17	50	0	33	0
XIV.....	0	33	22	22	22	0	0	33	0	0	33	33	0	33	33	0	33	0
Others....	17	30	39	6	17	1	29	30	6	6	18	12	8	8	16	8	62	0
Group IV	5	26	27	22	18	3	14	28	26	8	16	10	4	10	14	21	42	11
All types..	12	27	28	17	15	1	9	33	26	13	14	5	3	12	25	24	34	2

* The duration of the uncomplicated febrile state is the number of days from onset to the last febrile temperature (over 99 F.) before cure, death or recognition of complications, and includes any intervening afebrile intervals.

TABLE 12.—*Distribution (per Cent) of Patients by Outcome According to Number of Days Hospitalized for Pneumonia or Its Sequelae*

	Not Complicated										Complicated						
	Well				Dead						Well			Dead			
Type	1 to 6	7 to 10	11 to 14	15 and Over	1	2	3	4 or 5	6 to 8	9 to 14	15 and Over	1 to 10	11 to 14	15 and Over	1 or 2	3 to 7	8 to 14	15 and Over
I.....	5	37	26	32	18	24	12	27	12	3	3	8	9	83	27	27	23	23
II.....	6	23	27	43	18	12	12	30	18	12	0	20	7	73	8	32	16	42
III.....	10	19	25	46	20	15	20	13	22	10	0	0	27	73	42	26	27	5
IV.....	3	27	32	38	30	30	10	10	10	10	0	0	33	67	0	50	0	50
V.....	3	34	33	31	10	20	10	10	20	20	10	13	0	87	40	20	20	20
VI.....	11	34	28	28	0	0	43	29	14	14	0	0	0	100	50	50	0	0
VII.....	6	28	28	37	20	14	17	26	12	9	3	20	33	48	34	17	50	0
VIII.....	4	41	26	30	0	17	50	0	34	0	0	11	11	78	13	25	13	50
IX.....	4	28	20	48	0	0	0	80	0	20	0	0	33	67	..	..	..	..
XIV.....	0	22	22	56	0	33	67	0	0	0	0	33	33	33	..	..	..	..
Others....	8	23	20	44	12	29	18	24	0	12	6	0	22	78	0	25	25	50
Group IV	10	34	23	35	8	14	33	28	10	4	4	9	10	81	33	17	33	17
All types..	7	31	25	37	15	17	21	23	13	8	3	10	16	75	27	25	24	23

Type II pneumococci were recovered in material taken from a total of 104 patients during the five year period, and this was the fifth most

frequent type during 1937-1938. Type II pneumonia carried a suggestively higher mortality rate than did type I, but there was no difference in their complication rates. Concomitant conditions, present in one third of the patients, were accompanied by an elevation in the death rate as compared with that for patients in whom they were not recognized. About two thirds of all complications involved the pleura, as was true with type I, but otitis media was rarely observed. The heart and pericardium, however, were more frequently involved than in disease due to any other type.

Compared with patients having pneumonia of type I, a suggestively greater proportion of those with type II were Mexican and the incidence of males was slightly increased. There was no observed difference between the two types in the distribution according to age or season or in the complaints preceding the onset of pneumonia. For type II, the major symptoms of pneumonia were more frequently cough and

TABLE 13.—*Incidence (per Cent) of Patients Who Had a Defervescence with No Subsequent Recurrence of Fever Before Cure, Death or Recognition of Complications (Tabulated According to Outcome)*

Type	Not Complicated		Complicated	
	Well	Dead	Well	Dead
I	36	9	19	13
II	28	0	25	8
III	24	6	13	5
VII	33	3	24	0

bloody sputum and less often fever and chill. Few of the pulmonary lesions were distinctly atypical (only 6 per cent), but 23 per cent of the more typically lobar lesions involved two lobes and 18 per cent three or more lobes—a more extensive pulmonary involvement than that found in pneumonia of any other type. This evidence of the invasive powers of type II pneumococci was confirmed by an observed increase of 20 per cent [6] in the incidence of bacteremia as compared with that associated with type I.

Compared with the temperature of patients with type I pneumonia, that of patients with type II was lower, exceeding 103.5 F. in a significantly smaller proportion, while the febrile course tended more often to be horizontal and the fluctuations to be somewhat greater. There was less often a recurrence of fever following the defervescence (except in patients with complications who survived). The febrile course was longer in patients without complications, and complications developed

6. No statistical significance may be attached to that difference, however, because of the small number of patients studied and the special circumstances under which the cultures were usually taken.

earlier in the disease. The period of hospitalization was greater for type II than for type I, in the case of all patients except those surviving and having no complications.

Type III pneumonia was the third most common type during 1937 and 1938. During the five year period there were 190 patients, of whom 58 per cent survived without complication (the optimum outcome rate being lower for types II and III than for any other type), 34 per cent died (the mortality for types III and VI exceeding that for any other type) and 18 per cent had complications (10 per cent dying with complication). Concomitant conditions were recognized in over half the patients. Of the complications observed, only 57 per cent were pleural (22 per cent empyema and 35 per cent pleural effusion). It is interesting to examine the relation between the gross incidence of all pleural involvement and the frequency with which such involvement was found to be infected (empyema), as shown in table 14 for types I, II, III and VII. These data suggest but by no means prove that the less often the pleura is clinically involved, the less often is such involvement likely to be an empyema.

TABLE 14.—*Incidence (per Cent) of Pleural Involvement Among All Complications and of Empyemas Among Pleural Involvements*

Type	Pleural Among All Complications, per Cent	Empyemas Among Pleural Complications, per Cent
I	68	71
II	63	54
III	57	39
VII	58	17

The usual seasonal trend was exaggerated for pneumonia of type III. The age distribution was higher than for any other type, 65 per cent of the patients being over 40 years of age and 35 per cent over 60. A suggestively smaller proportion of the patients were asymptomatic prior to the onset, while the unfolding of symptoms following the onset was even more rapid than in type I or II. Atypical lesions were much more frequent than in type I or II, but the more typically lobar lesions were no less extensive than for type I. Bacteremia was found to occur in 12 per cent of the 26 patients in whose cases cultures were made. The temperature at the time of admission was definitely lower than in types I and II, the general appearance of the chart being similar to that of type II. It is interesting to note that patients surviving without complication ran a longer febrile course, while among those dying and having no complications death tended to occur earlier in patients with type III pneumonia than in those with type I or II. Complications developed at about the same time following the onset as in patients with type I.

Type VII pneumonia was second in frequency during 1937 and 1938 and was represented by 172 patients. Half of these had concomitant conditions, and 70 per cent received serum therapy. In 16 per cent complications developed, 24 per cent died and 64 per cent survived without complications (4 per cent died with complications). Excluding types VI and XIV, more of the complications associated with type VII pneumonia were pleural effusion and fewer were empyemas than those accompanying any other type, the total of pleural involvements being the same, however, as with type III.

The curve of age incidence was symmetric for type VII pneumonia. Complaints preceding the onset were similar to those associated with type I, while of the major symptoms, chill and fever occurred with the same frequency as in type III, cough and bloody sputum as in type II infections and painful respiration and dyspnea as in type I. The concurrence of symptoms paralleled that for types I and II, but the symptomatic maximum was not reached so rapidly. The lesion was distinctly atypical in 11 per cent of the patients, while a third of the more typical lesions extended over more than one lobe. Bacteremia was demonstrated in 15 per cent of the 26 patients studied. On the average the leukocyte count was about the same as for type I and the temperature on admission as for type II, while the general febrile course lay between those for types I, II and III. Among half of the patients who died without complications, death occurred between the eighth and the tenth day of illness. Over half of the patients with complications who survived required hospitalization for less than two weeks (reflecting the high incidence of simple pleural effusions), while among all the patients who had complications and died, death occurred within two weeks of admission.

It is rather natural to assume that types which frequently produce atypical lesions are likely to be less "virulent" than those which usually cause typically lobar pneumonia. Such a view is untenable, however, on the basis of the data presented in table 15, in which it is seen that the incidence of atypical lesions is apparently not related to their mortality rate, to the extent of lobar lesions or to the mortality rate for lobar lesions in one lobe.

The remaining types are of profound interest to students of pneumonia. In this series, however, the numbers of patients are too small to warrant a textual outline of the findings. The data concerning types IV, V, VI, VIII, IX and XIV are included in tables 2 through 12 for the benefit of those especially concerned with pneumonia. The types which are pooled as "others" are enumerated in table 16.

Data concerning the complications of pneumonia are presented in table 17. Of all complications, 61 per cent involved the pleura (33 per cent being empyema), 12 per cent the middle ear, 8 per cent the heart and pericardium, 7 per cent the endovascular system and 5 per cent the

TABLE 15.—*Cooper Types in Order of Frequency with Which They Produced Atypical Lesions; Percentage of Atypical Lesions Among All Lesions and of One Lobe Lesions Among All Lobar Lesions, and Mortality Rates for One Lobe and for Atypical Pneumonia* *

Type	Per Cent Atypical Among All	1 Lobe per Cent Among Lobar	Mortality per Cent	
			Atypical	1 Lobe Lobar
I	3	66	27	8
II	6	57	50	14
VII	11	67	42	13
V	15	66	33	15
IV	19	85	20	21
VIII	19	78	8	15
IX	20	84	14	8
XIV	27	73	75	0
III	33	67	38	20
VI	40	60	36	10
Others	40	77	20	9

* The group for each type except III and "others" included less than 20 patients with atypical pneumonia; there were more than 20 with one-lobe lobar pneumonia in the group with each type except VI and XIV. Actual numbers may be computed from tables 1 through 12.

TABLE 16.—*Enumeration of "Other" Types, Showing Total Number of Patients, Number Dead and Number with Complications*

Type	Total Number of Patients	Number Dead	Number with Complications
X	3	1	0
XI	11	2	2
XII	14	1	1
XIII	2	0	0
XV	13	5	1
XVI	7	1	1
XVII	12	3	1
XVIII	10	0	0
XIX	10	2	2
XX	7	2	1
XXI	2	0	0
XXII	4	0	1
XXIII	9	1	1
XXIV	2	0	1
XXV	7	1	0
XXVII	1	0	0
XXVIII	2	2	1
XXIX	5	0	0
XXXII	1	0	0
Total	122	21	13

meninges. Except among patients with otitis media or thrombophlebitis, the mortality was higher in the presence than in the absence of complications. Although in only 19 per cent of all (1,469) patients did complications develop, 33 per cent of those in whom they occurred had more than one complication. The distribution of patients with complications according to age, sex and leukocyte count did not differ remarka-

bly from that of patients without complications. Among patients with complications, the blood cultures were more frequently positive, concomitant conditions were slightly less common and serum was somewhat more often administered.

During recent years there has been an increasing tendency to classify pneumococcic pneumonia etiologically. One may question whether this trend owes more to a realization of fundamental differences between the types than to use of type-specific serum. The practical importance of classification according to types is minimized by the fact that there is such a large number of them that it is impossible to bear in mind the

TABLE 17.—*Complications of Pneumonia* *

Complication	Incidence per Cent Among All Complications	Deaths, per Cent	Distribution (%) of Patients According to Type of Organism ‡							According to Pulmonary Lesion		
										Lobar		
			I	II	III	IV	V	VII	VIII	1 Lobe	2+ Lobes	Atypical
Empyema	33	34	40	11	7	3	8	3	5	47	43	9
Pleural effusion	28	26	19	11	14	2	1	15	6	60	36	4
Otitis media	12	10	43	3	2	3	5	8	13	68	18	16
Meningitis	5	100	6	17	17	6	6	6	17	32	39	28
Pulmonary abscess	4	69	15	0	8	8	8	8	15	38	54	8
Acute endocarditis	4	100	15	31	0	8	15	8	0	38	54	8
Pericarditis	3	78	0	33	0	33	0	0	0	22	67	11
Thrombophlebitis	3	0	21	11	0	0	0	0	11	33	67	0
Embolism	2	75	13	13	13	0	13	25	0	50	50	0
Pericardial effusion	1	67	0	33	0	0	0	0	33	33	67	0
Other complications §	4	50	29	0	7	0	0	29	14	50	36	14
All patients with complications †	..	53	27	10	12	3	5	10	6	52	37	10
No known complication	..	20	21	6	13	4	4	12	4	57	25	19

* Patients with more than one complication are listed once under each.
† Each patient is listed here once only.
‡ Only the more common Cooper types are listed; the unlisted types (VI, IX to XXXII and group IV) bring the total to 100 per cent.
§ Listed with the number of cases and, in parenthesis, the number of deaths, the "other complications" were: mediastinitis 2 (2); mastoiditis 2 (1); parotitis 2 (1); subcutaneous abscess 2 (1); pneumococcic arthritis 1 (1); lateral sinus thrombosis 1 (1); bronchiectasis 1 (0); hydropneumothorax 1 (0); massive pulmonary fibrosis 1 (0), and suppurative lymphadenitis 1 (0).

characteristics of each. One may also inquire whether other factors, such as the character of the lesion or the presence of concomitant conditions may not be of greater prognostic importance than the type of organism.

In tables 18, 19, 20 and 21 are presented the incidence and outcome for the variables which were used to characterize pneumonias associated with the various types of organism, along with the distribution of the types and the incidence of concomitant conditions and of serum treatment. Certain of the findings are summarized in the following paragraphs.

A peak in the age incidence was observed in the figures for the decade 30 to 39, while almost 60 per cent of the patients were between

20 and 50 years of age. With the exclusion of the first decade,[7] the mortality rate rose and the optimum outcome rate declined with increasing age, while the complication rate remained relatively constant (a peak may be suspected in the forties). The proportion of cases of pneumonia due to organisms of types I and II fell off with advancing age, while infection with types III and VIII increased in frequency. The incidence of concomitant conditions increased with age, but the same changes in incidence and outcome were noted for patients without known concomitant conditions as for all patients. Although the frequency of serum treatment declined with increasing age, the change may be ascribed entirely to the changing type distributions (table 18).

Three fourths of the patients were Caucasian, and a fifth were Mexican.[8] Concomitant conditions were less commonly recorded among the latter (perhaps because of limitations in the histories due to difficulty with language), and there was a definite increase in the incidence of pneumonia of types II and VII. The complication rate was suggestively lower and the optimum outcome rate higher among Mexicans than among Caucasians, but the mortality rates were equal. Only 8 per cent of the patients were Negroes, and among them type I was less commonly the causative organism. There was a significant increase in the mortality rate of Negroes over that of Caucasians, but the complication and optimum outcome rates were not altered. Fifteen patients were of other races, largely far Eastern. The difference between the outcome among them and that among other races carries little statistical weight (table 18).

Sixty-five per cent of the patients were men. Their mortality rate definitely exceeded that of the women, a difference that cannot be explained on the basis of type distribution, incidence of serum treatment or concomitant conditions (table 18).

In 43 per cent of the patients the history either made no mention of complaints preceding the onset of pneumonia or definitely stated that they were absent, while in 48 per cent there were complaints indicating that some infection of the respiratory tract preceded the onset. The latter group had a suggestively lower mortality rate. Associated conditions were present in most patients with prodromal symptoms referable to a system other than the respiratory or the gastrointestinal, the mortality rate being somewhat elevated and the rarer types more common than usual (table 19).

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7. One may not accept at face value either the incidence or the outcome for infants and children, since typing was attempted in their cases only when the children were exceptionally ill or had complications which made the recovery of organisms relatively easy.

8. Of the entire hospital population, about 20 per cent are usually Mexican and 7 per cent Negro.

TABLE 18.—*Outcome Attending Variations in Month, Age, Race and Sex*

	Variable	Total No. of Patients	Incidence (%)	Outcome (%)			Distribution (%) by Type ‡								Concomitant Conditions (%)	Serum Therapy (%)
				Optimum †	Death	Complication	1	2	3	5	7	8	Other Cooper Types	Group IV		
Month	January	241	16	65	21	20	17	9	16	7	14	4	14	20	50	36
	February	228	16	61	25	20	20	7	14	4	10	4	19	24	44	29
	March	161	11	65	20	23	19	7	12	3	12	4	11	32	43	35
	April	143	10	68	22	16	30	5	7	6	15	3	14	19	47	41
	May	65	4	71	17	17	29	6	12	1	6	5	15	23	57	42
	June	69	5	59	25	26	26	4	9	3	12	3	23	20	54	41
	July	57	4	65	23	23	26	4	19	5	11	5	15	16	49	47
	August	43	3	70	14	16	12	21	9	5	12	0	18	23	40	40
	September	50	3	72	18	16	22	8	14	2	8	8	28	10	66	40
	October	80	5	63	25	21	23	9	13	3	9	6	22	18	58	40
	November	113	8	61	29	17	22	5	10	3	12	9	30	10	57	45
	December	219	15	66	24	15	22	6	15	4	13	6	17	17	56	46
Age (Yr.)*	0 to 9	26	2	27	15	54	50	4	0	8	12	0	16	12	38	19
	10 to 19	163	11	77	9	17	28	11	8	4	14	2	15	18	31	45
	20 to 29	282	19	76	8	18	27	9	7	5	10	3	12	26	43	48
	30 to 39	324	22	66	20	19	23	6	10	4	10	4	20	23	49	40
	40 to 49	261	18	62	24	21	21	8	9	5	13	4	17	22	49	40
	50 to 59	199	14	56	38	18	18	7	16	1	14	8	19	19	61	34
	60 and over	214	15	54	40	14	10	2	31	4	10	8	23	11	72	28
Race	Caucasian	1,071	73	64	21	20	23	6	13	4	11	5	19	20	53	40
	Mexican	261	18	69	20	15	22	11	12	5	15	3	12	21	39	40
	Negro	122	8	60	29	20	15	6	11	2	12	4	26	24	54	28
	Others	15	1	40	33	33	7	7	27	0	7	13	20	20	53	40
Sex	Male	961	65	63	25	19	22	8	13	4	12	3	17	19	48	41
	Female	508	35	68	18	19	21	5	14	4	11	5	17	23	55	35

* In the first decade typing was attempted only under special circumstances.
† In this and the other tables "optimum" means survival without complication.
‡ Arabic numerals indicate Cooper types.

TABLE 19.—*Analysis of Histories with Respect to Complaints Before Onset,* to Days Between Onset and Admission and to Nature, and Duration of Symptoms*

Variable		Total No. of Patients	Incidence (%)	Outcome (%)			Distribution (%) by Type								Concomitant Conditions (%)	Serum Therapy (%)
				Optimum	Death	Complication	1	2	3	5	7	8	Other Cooper Types	Group IV		
Complaints prior to onset †	None	626	43	64	24	18	25	8	12	4	14	4	14	20	45	40
	Infection of the upper respiratory tract	655	45	68	19	20	21	7	15	4	11	5	16	21	48	39
	Malaise	49	3	59	20	25	29	4	8	2	10	0	12	35	43	45
	Gastrointestinal	22	1	64	18	18	23	5	9	0	14	5	37	9	68	50
	Others	117	8	55	37	17	8	5	12	6	8	6	44	12	91	29
Number of days from onset to admission	1	265	18	70	17	18	20	6	14	5	9	6	28	13	62	42
	2	182	12	75	17	12	24	8	13	2	13	3	19	19	48	46
	3	231	16	64	20	22	26	8	8	4	10	6	15	22	49	39
	4	205	14	66	24	15	18	8	15	3	15	3	15	22	41	38
	5	176	12	69	18	16	27	5	14	5	11	4	14	21	40	40
	6	84	6	58	27	23	21	11	8	10	13	6	7	23	46	44
	7	153	10	56	31	27	19	7	15	5	15	5	11	24	52	35
	8	26	3	73	12	19	38	0	12	4	15	4	8	19	38	46
	9	10	1	50	30	30	40	10	10	0	10	0	10	20	50	50
	10	25	2	44	36	24	20	12	20	0	20	0	12	16	64	24
	11 and more	80	5	58	33	23	13	5	14	1	13	6	30	20	60	21
	?	32	2	28	59	34	12	6	22	0	0	6	12	41	53	16
Major symptoms of pneumonia ‡																
A. Symptoms	Pain on respiration	591	82	68	17	19	27	10	11	3	12	3	13	22	..	42
	Fever	554	77	69	15	20	30	9	10	3	10	4	12	21	..	43
	Chill	478	66	72	15	17	29	9	11	3	12	4	12	21	..	45
	Cough	456	64	68	17	18	26	10	12	2	13	4	12	22	..	41
	Bloody sputum	319	44	66	19	19	24	11	12	3	14	3	12	22	..	44
	Dyspnea	169	23	58	20	30	30	9	7	5	12	3	13	21	..	42
B. Number of symptoms per patient	None	15	2	27	40	60	13	7	13	13	0	13	0	40	..	27
	1	31	4	55	19	29	26	10	23	6	13	0	12	10	..	26
	2	98	14	71	13	17	26	10	11	5	11	4	12	20	..	36
	3	187	26	61	21	26	26	9	11	1	12	2	14	25	..	40
	4	216	30	73	13	19	32	9	9	3	12	3	9	24	..	46
	5 or 6	177	24	67	19	16	25	10	13	4	12	4	15	18	..	43
C. Number of days between onset of first and last symptom	0 or 1	524	72	66	19	21	27	10	12	3	10	3	11	23	..	39
	2 or 3	114	16	78	7	16	27	8	9	4	14	4	15	20	..	47
	4 to 6	60	8	55	18	30	33	10	10	7	25	0	5	10	..	50
	7 and over	26	4	58	31	23	15	15	4	0	8	0	24	35	..	35

* Onset is defined as first appearance of chill, fever, pain on respiration, bloody sputum, dyspnea, prostration or coma, or, in their absence, of sudden change for the worse during an infection of the respiratory tract.
† Complaints preceding the onset are studied for all patients.
‡ Only patients without known concomitant conditions were studied. The terms "chill," "cough" and "bloody sputum" are explained in the footnote to table 6.

The major symptoms of pneumonia were studied only in the histories of patients without known concomitant conditions. Cough being disregarded if it was present before the onset of pneumonia, the symptoms in the order of frequency were: pain on respiration, fever, chill, cough, bloody sputum and dyspnea. In patients who complained of dyspnea complications developed more often, a difference which carries considerable statistical weight and cannot be ascribed to the type distribution. Five or all six of these symptoms were present in 24 per cent of the patients, at least four in 54 per cent and at least three in 80 per cent. Three fourths of the patients reached their symptomatic maximum within the first day of the disease, but in them the outcome was considerably worse than in patients whose symptoms developed over a period of two or three days (table 19).

Thirty per cent of the patients were admitted within two days of the onset of pneumonia, 60 per cent within four days and 76 per cent within seven days, the average interval being four and seven-tenths days (table 19). The mortality and complication rates rose with increasing delay in admission, but since many of the patients received serum, the effectiveness of which declines with delay in administration, it became important to study the outcome in patients who did not receive serum (these are not controls for the treated group, however). The results of that observation are given in table 22. It is apparent that the day of admission is considerably less important when serum treatment is not given than when it is given.

The pulmonary involvement was rather typically lobar in 84 per cent of all patients. Of the lesions in this group, 68 per cent were confined to one lobe and 20 per cent to two lobes, while 12 per cent extended over three or more lobes. Only 17 per cent of the patients had lesions that were distinctly atypical clinically or found to be atypical at autopsy when they had been suspected ante mortem of being so. Of these, 29 per cent were minimal (that is, confined to a small area, usually at the base of one lung), 47 per cent moderate (usually involving the bases of both lungs or a considerable single area) and 24 per cent extensive (usually involving a large proportion of the lung). Concomitant conditions were more common in association with atypical than with lobar lesions, regardless of their extent; they were also found to be increasingly common with increasing extent of the lesion, regardless of its character. The incidence of pneumonia of types I, II and VII was considerably greater in patients who had lobar than in those who had atypical lesions, while the incidence of type III pneumonia and of the rarer types was greater in patients who had atypical lesions. Serum was much more often administered when the involvement was lobar. The outcomes are of great interest. Arranged with respect to outcome, from best to worst,

the lesions were: minimal atypical; one lobe lobar; moderate atypical; two lobe lobar; extensive atypical, and lobar lesions of three or more lobes (table 20).

Blood cultures were usually taken under special circumstances, and one may not accept either the incidence or the outcome as representative. One may accept the difference in outcome between patients with demonstrated bacteremia and those with negative cultures, however, the difference being similar to that usually reported (table 20).

The average total leukocyte count, made during the acute pneumonia, was slightly under 19,000, half of the counts being between 10,000 and 20,000. Patients with counts under 5,000 had extremely poor outcomes, which would be consistent with destruction of the cells at a rate exceeding their production. No difference in outcome, type distribution or incidence of concomitant conditions was found between that group of patients and those with counts over 5,000 (table 20).

The temperature at the time of admission exceeded 103.5 F. in 27 per cent of the patients, 102.5 F. in 56 per cent and 101.5 F. in 79 per cent. The incidence of concomitant conditions and of type III pneumonia fell off with increasing degrees of fever, while types I and II tended to become relatively more common. The mortality rate diminished with increasing fever, the complication rate showing, if anything, a slight tendency to rise. These same alterations in outcome in relation to temperature on admission were found in patients without known concomitant conditions (table 21).

Almost three fourths of the patients had a febrile course [9] that could be described as "in general either horizontal or falling, with moderate fluctuations." The general trend, or slope, of the temperature curve was downward (better) for 60 per cent of the patients, horizontal for 29 per cent and upward (worse) for 11 per cent. The fluctuations were moderate for 81 per cent, insignificant for 15 per cent and marked for only 4 per cent. Regardless of the extent of the fluctuations the outcome was best when the trend was downward and worst when it was upward; and regardless of the general trend the outcome was probably best when the variations were minimal and worst when they were marked (table 21).

The average time from the onset to the first normal temperature was seven and six-tenths days with 41 per cent of the patients becoming afebrile for the first time between the fifth and the eighth day. The outcome tended to become worse with increasing duration of continuous fever. Almost half the patients died who had no defervescence [9] (table 21).

9. All aspects of the temperature are considered only for the interval before the recognition of complications, if any.

TABLE 20.—*Analysis of Diagnosis, Blood Culture and Leukocyte Count*

	Variable	Total No. of Patients	Incidence (%)	Outcome (%)			Distribution (%) by Type								Concomitant Conditions (%)	Serum Therapy (%)
				Optimum	Death	Complication	1	2	3	5	7	8	Other Cooper Types	Group IV		
Pulmonary involvement																
Lobar (No. of lobes)	1	823	57	73	13	18	25	7	10	4	13	5	17	21	37	43
	2	257	17	56	27	22	27	9	11	4	12	4	11	21	42	44
	3 and over	140	10	28	61	34	26	13	10	4	14	5	7	21	51	44
Atypical	Minimal	69	5	91	7	3	4	3	28	3	6	9	23	23	62	12
	Moderate	124	8	61	26	10	3	1	21	3	8	2	41	20	77	19
	Extensive	56	4	36	59	27	7	5	32	5	9	7	24	11	80	23
Blood culture	Positive *	33	14	24	67	45	24	15	9	6	12	12	12	9	61	58
	Negative †	209	86	66	22	23	37	6	11	3	11	6	22	5	53	65
	Cultures	242	16	60	28	26	35	7	11	4	11	6	21	5	54	64
	No cultures	1,227	84	66	22	18	19	7	13	4	12	4	17	23	50	34
Maximum recorded total leukocyte count (in thousands)‡	1 to 4	12	1	25	75	8	17	17	17	0	17	8	8	17	75	25
	5 to 9	123	14	68	21	14	18	9	14	1	12	2	24	20	54	40
	10 to 14	227	24	64	20	22	21	9	11	5	12	6	16	18	51	47
	15 to 19	230	24	70	17	20	22	9	10	6	11	7	14	22	52	38
	20 to 24	154	16	65	19	20	21	9	12	3	10	5	16	23	49	38
	25 to 29	89	9	63	19	24	20	8	11	2	10	4	16	26	48	39
	30 and over	104	11	66	20	24	23	4	18	6	11	5	15	19	47	46

* One or more cultures positive.

† All cultures negative.

‡ The figures are for 939 patients during acute illness.

TABLE 21.—*Analysis of Temperature Prior to Recognition of Complications, of the Duration of Hospitalization and of the Treatment* *

	Variable	Total No. of Patients	Incidence (%)	Outcome (%)			Distribution (%) by Type								Concomitant Conditions (%)	Serum Therapy (%)
				Optimum	Death	Complication	1	2	3	5	7	8	Other Cooper Types	Group IV		
Temperature on admission	To 99	48	3	50	42	15	13	4	25	4	6	6	21	21	65	15
	100	90	6	57	34	19	12	8	20	3	13	7	21	17	60	27
	101	161	11	61	24	17	17	5	9	5	10	7	22	25	55	30
	102	336	23	60	26	18	17	5	15	3	12	5	20	23	56	34
	103	430	29	70	18	18	21	10	13	4	13	5	14	21	52	40
	104 and over	403	27	64	19	23	32	7	10	4	12	3	14	16	39	50
Trend																
Insignificant fluctuations	Plateau	61	4	56	36	18	28	13	11	3	10	7	8	20	41	44
	Better	130	9	82	11	11	28	5	8	5	14	5	13	23	51	45
	Worse	34	2	41	59	6	26	0	15	12	15	6	9	18	53	47
Moderate fluctuations	Plateau	338	23	50	37	25	19	7	16	4	11	4	20	20	49	33
	Better	712	49	76	6	17	23	7	13	3	11	5	20	20	49	41
	Worse	128	9	24	68	18	16	9	13	4	15	5	18	20	66	37
Marked fluctuations	Plateau	31	2	29	45	48	10	13	13	6	3	6	22	26	58	16
	Better	31	2	71	6	26	29	6	3	6	10	3	13	29	45	29
	Worse	4	0	0	100	50	0	0	25	25	25	0	0	25	75	50
Number of days from onset to first normal temperature	1	21	2	86	14	0	10	5	33	0	0	19	24	10	52	38
	2	64	4	77	16	11	19	2	14	3	8	8	30	17	63	47
	3	93	6	83	9	10	30	5	9	3	15	10	22	6	55	62
	4	104	7	80	10	13	25	13	9	6	10	3	20	15	49	45
	5	149	10	64	15	18	23	7	11	5	14	2	17	20	51	48
	6	159	11	77	12	18	26	8	14	3	12	3	19	17	42	45
	7	151	10	78	14	11	21	9	11	5	13	5	20	23	51	54
	8	144	10	74	10	19	24	7	12	5	10	6	17	19	49	37
	9	96	7	73	9	19	26	6	14	4	16	5	11	18	39	44
	10	67	5	69	9	25	16	3	12	3	22	4	12	27	37	28
	11 and over	214	15	66	12	29	18	7	12	4	9	5	16	29	54	27
	? or no defervescence	207	14	7	88	25	17	8	18	4	10	4	16	23	59	29
Manner of defervescence	Crisis	646	44	75	14	16	24	7	13	5	13	5	17	16	48	47
	Lysis	632	43	74	10	20	21	6	12	3	11	5	19	25	50	32
	No defervescence	191	13	2	95	26	18	8	17	4	11	4	17	20	58	31
Recurrence of fever	Yes	915	72	71	15	19	22	7	14	4	12	4	18	18	52	40
	No	363	28	83	4	15	25	3	9	4	12	6	15	25	42	40

Number of days from onset to last febrile temperature	1 to 4	140	10	79	17	6	24	6	10	6	9	6	22	14	51	52
	5	107	7	61	28	15	19	11	15	4	11	4	23	14	50	41
	6	120	8	73	21	8	23	5	9	4	11	4	21	23	45	44
	7	149	10	73	25	7	23	6	15	5	9	3	19	19	51	38
	8	146	10	66	26	15	22	5	12	2	13	5	20	22	49	36
	9	133	9	63	23	21	20	5	14	6	15	5	13	15	49	50
	10	119	8	70	17	19	17	9	14	3	15	8	18	16	44	34
	11	83	6	70	22	13	27	7	13	2	12	2	9	25	58	33
	12	69	5	62	14	26	17	12	10	6	19	6	9	20	52	38
	13 or 14	96	6	61	16	29	24	7	24	1	13	4	5	22	47	28
	15 and over	275	18	54	23	34	19	8	10	4	9	5	20	24	53	37
Number of days in hospital for pneumonia or its sequelae	1	48	3	0	100	27	19	8	29	2	17	2	10	12	60	37
	2	53	4	0	100	23	21	4	19	8	11	2	19	17	64	34
	3	60	4	5	95	10	10	3	20	2	10	7	15	33	68	25
	4	41	3	29	71	15	12	10	10	2	22	0	27	17	49	32
	5	54	4	24	74	17	22	11	17	0	4	2	19	26	50	24
	6	51	3	63	29	6	16	6	18	4	16	4	12	25	41	49
	7	82	6	79	17	7	23	6	7	6	11	7	17	22	44	39
	8	97	7	86	12	7	36	6	7	5	10	8	9	17	47	53
	9	79	5	78	15	13	27	8	15	6	11	4	14	16	40	43
	10	98	7	86	9	9	15	5	8	2	13	6	24	26	47	36
	11 to 14	285	19	83	6	13	22	7	12	5	14	5	17	18	49	38
	15 to 21	262	18	85	5	13	21	10	11	3	12	3	20	19	49	40
	22 and over	261	18	51	5	48	23	6	13	4	8	7	16	21	55	39
Treatment																
Oxygen	Yes	932	63	54	32	22	24	7	13	4	12	4	17	18	51	44
	No	537	37	83	7	13	18	7	13	4	10	6	18	24	50	30
Sulfanilamide	Serum															
Yes	No	87	6	76	10	16	3	1	24	2	5	11	53	0	64	0
No	Yes	482	33	66	20	21	46	11	5	7	21	4	7	0	47	100
Yes	Yes	87	6	69	18	22	30	11	14	3	24	7	11	0	51	100
No	No	813	55	62	21	18	8	5	16	2	6	4	21	37	51	0
Yes	Yes/no	174	12	72	14	19	17	6	19	3	14	9	32	0	57	50
No	Yes/no	1,295	88	64	24	19	22	7	12	4	11	4	17	23	50	37
Yes/no	Yes	569	39	66	19	21	44	11	6	7	21	4	6	0	47	100
Yes/no	No	900	61	64	25	17	8	4	17	2	6	5	25	33	53	0

* The significance of the terms used in the table is as follows: "normal" means a temperature of 99 F. or less; "fever," over 99 F. The temperature on admission is the maximum during the first few hours in the hospital. The febrile course was determined by the appearance of the chart: among the terms describing trend, or general slope, is "plateau" meaning horizontal, "better," falling and "worse," rising. Fluctuations, or variations termed "insignificant" were usually of less than 1 degree; "moderate," usually from 1 to 3 degrees, and "marked," usually over 3 degrees. "Crisis" signifies fall from peak to normal during twenty-four hours or less. "No defervescence" means none prior to cure, death or complication; 3 patients left the hospital apparently almost cured though still febrile, and were listed as having "optimum" outcome. Recurrence of fever was studied only for patients who had a defervescence.

Crisis and lysis occurred with nearly equal frequency, the mortality rate being slightly lower in patients with lysis and the complication rate slightly lower in those with crisis. There were 562 patients not treated with serum who survived without complication, and a further analysis was conducted on them. It was found that the incidence of crisis fell off as the time from the onset to the first defervescence increased (from 65 per cent for patients with early defervescence to about 30 per cent for those with late defervescence), while the incidence of recurrence of fever remained virtually constant for various intervals from the onset to the first normal temperature. There was a recurrence of fever in 74 per cent of the patients who had a crisis and in 62 per cent of those who had a lysis. The first defervescence had been by crisis in 48 per cent of patients who had a recurrence of fever and in 35 per cent of those who did not have a recurrence. Among all patients who received no serum, in those with crisis the mortality rate was 16 per cent while in those with lysis it was 10 per cent. Some of the foregoing findings may be generalized as follows: The longer the patient is continuously febrile, the less likely is the defervescence to be by crisis; early defervescence is not more likely to be followed by a recurrence of fever than is late; a crisis is more likely to be followed by a recurrence than is a lysis; crisis carries less assurance that the patient will survive than does lysis, but slightly more assurance that he will avoid complications. In table 2 it is seen that there was a defervescence (before recognition of the complications) in almost all patients who had complications but survived and in only half of those who died with complications. It is probable, then, that the development of complications before the temperature has fallen below 99.0 F. is much more serious than if the complication develops after a defervescence (table 21).

The number of days from the onset to the last febrile temperature (before cure, death or recognition of complications) was observed over a range of from one to one hundred and fifty-three days (careful study failed to reveal complications in these patients with prolonged fevers), the general average being eleven and one-tenth days. For patients surviving without complication the average was ten and three-tenths days (most frequently seven); for those dying without complication, nine and five-tenths days (most frequently 7); and for all patients with complications, sixteen and two-tenths days (most frequently nine). As the duration of the fever increased there was a definite increase in the complication rate but no great change in the mortality rate (table 21). In table 23 are shown the results of a further study of the total duration of fever. It is clear from this table that the time element is of great importance in determining the character of an unfortunate outcome: whether it will be death or complication or both.

The duration of hospitalization for pneumonia and its sequelae extended over a range of from one to two hundred and seventy days, being from ten to twenty-one days for 39 per cent of the patients. The general average was fourteen and four-tenths days. For patients surviving without complication the average was fourteen and four-tenths days and for those dying without complication four and eight-tenths days; for patients surviving with complication it was forty-one and four-tenths days and for those dying with complication ten and one-tenth

TABLE 22.—*Days from Onset to Admission for Patients Without and With Serum, Giving the Number of Patients and the Outcome (per Cent)*

Number of Days From Onset to Admission	No Serum				Serum			
	Number of Patients	Outcome (%)			Number of Patients	Outcome (%)		
		Optimum	Death	Complication		Optimum	Death	Complication
1 to 3	394	65	22	18	284	75	12	18
4 to 6	279	68	23	13	186	62	22	23
7 and over	200	59	28	26	94	51	34	30

TABLE 23.—*Rate (per Cent) of Complication Among Patients Who Died and of Deaths Among Those with Complication, According to Days of Fever from Onset to Complication or Death*

Total Days of Fever	Complication (%) Among Those Who Died	Death (%) Among Those with Complication
0 to 4	8	25
5 or 6	13	27
7 or 8	21	50
9 or 10	32	31
11 or 12	21	21
13 or 14	40	21
15 to 19	30	29
20 to 29	68	42
30 and over	80	30

days (table 21). During 1937 and 1938, the average daily cost per inpatient in this hospital was $4.71; on that basis alone patients surviving with complications cost about $127 more per patient than did those surviving without complication—a figure that fails to take into account special services demanded by complications.

A section of table 21 is given to treatment. It is impossible to draw from those data any conclusion concerning the relative or absolute merits of sulfanilamide,[10] oxygen and serum. Much more detailed study is required, this having been attempted for serum in an investigation reported on in another paper.

10. In the only patient to receive sulfapyridine meningitis had already developed.

SUMMARY

The records of 1,469 patients with pneumococcic pneumonia were analyzed in an effort to determine the character of pneumonia caused by the various types of pneumococcus and the effect of certain variables in the patient and in the febrile course of the disease on the outcome. A brief study of the complications was also conducted. The effect of concomitant conditions and of serum therapy will be investigated and reported in subsequent papers.

Mary C. Moore and Josephine Abraham lent valuable assistance in the analysis of data.

Dr. J. Leonard Moore and Dr. Barclay E. Noble aided in the preparation of this paper.

PNEUMOCOCCIC PNEUMONIA

ANALYSIS OF THE RECORDS OF 1,469 PATIENTS TREATED IN THE LOS ANGELES COUNTY HOSPITAL FROM 1934 THROUGH 1938

II. OUTCOME AND CHARACTER OF PNEUMONIA IN THE PRESENCE OF ASSOCIATED OR CONCOMITANT CONDITIONS

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LOS ANGELES

Among the variables [1] which determine the character and outcome of pneumonia, one of the most important is the presence of concomitant conditions. In this paper are published the results of a study of the records of 1,469 patients, in 742 of whom some associated or concomitant condition was recognized.

MATERIAL AND METHODS

A concomitant condition is considered as any condition, barring pneumonia and its sequelae, the presence of which was indicated by any part of the patient's record. (If the records had been ideally complete, there would have been few if any patients without such conditions.) The original clinical, laboratory and nursing records of all (1,469) patients with pneumococcic pneumonia from 1934 through 1938 were abstracted in their entirety by some of the group of workers. One of us checked the abstracts with the original records, prepared the data for tabulation and supervised the analysis. Further details are given in the preceding paper.

We disregarded findings and diagnoses qualified by the word "doubtful" or "possible," all changes noted at autopsy that could not (except under the most extraordinary circumstances) be recognized ante mortem and the following miscellaneous conditions (each of which was almost always dwarfed in importance by some additional condition): asymptomatic goiter, asymptomatic prostatic hypertrophy, irregular menses, dysmenorrhea, nonbleeding uterine fibroids, retroversion of the uterus, senile vaginitis, Oxyuris in the urine, nocturia when less than three

This study was aided by a grant from the Pneumonia Fund of the School of Medicine, University of Southern California.

From the Department of Medicine, School of Medicine, University of Southern California, and from the Los Angeles County Hospital.

1. A study on the type of pneumococcus, the complications of pneumonia and certain variations in the patient and in the course of the disease has been made on these patients and presented in the first paper of this series.

times a night, "occasional slight jaundice," occasionally bloody stool, permanent colostomy of long standing, small ventral hernia, hydrocele, asymptomatic varicose veins, dental caries, diphtheria carrier, addiction to tobacco smoking, frequent headaches, cataract, parkinsonism, deaf-mutism and absence of patellar reflexes. When two conditions were present one of which was referable entirely to the presence of the first (e. g., bronchiectasis and chronic cough), the secondary condition was disregarded. If the conditions were independent, the patient was tabulated once under each condition in the enumeration of the conditions and was disregarded in the study of the character of pneumonia associated with each of the more important conditions. Some effort was made to evaluate the findings statistically; when the term "significant" is used it refers solely to such evaluation.[2]

OBSERVATIONS

Of the 1,469 patients, 727 were without known concomitant conditions; these formed the "control" group. The other 742 patients had 1,035 concomitant conditions, 523 patients having only 1 and 219 having more than 1 (averaging 2.3 per patient). An enumeration[3] of all observed conditions is given in table 1, showing the number of patients with each condition and the outcome (patients with more than one condition appearing once under each). In table 2 are presented data concerning the outcome and character of pneumonia associated with the more common conditions, in patients having only one known condition. The chart indicates the outcomes for certain groups shown in the two tables and (horizontal lines) those for the control group, with the standard errors. The findings concerning the more common conditions are briefly reviewed and discussed in the text.

CONDITIONS OF THE RESPIRATORY TRACT

Patients with histories of two or more attacks of pneumonia did not differ in outcome from patients with present evidence of bronchiectasis, and the two conditions were not infrequently observed together. Such patients were therefore combined to form a group of 45, in 31 of whom no other conditions were recognized. Comparison with the control group shows a significant increase in the optimum outcome rate (survival without complication), a significant lowering of the complication rate and a suggestive lowering of the mortality rate. In patients without other recorded conditions, the pulmonary involvement was less extensive than in the controls. Blood cultures were negative for the 6 patients in whose cases they were made. The apparent difference in racial distribution cannot account for the observed difference in outcome. The ages

2. For example, a "significant" difference in outcome between two groups means that the difference is probably not referable to the small number of patients but implies nothing as regards the other possible causes of the difference, such as age, type of organism and character and number of pulmonary lesions.

3. The conditions are enumerated because they were observed, not necessarily because they are considered important.

TABLE 1.—*Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed*

Concomitant Condition	Total No. of Patients	Outcome		
		Optimum	Death	Complication
Respiratory and oral				
"Asthma"	54	36	14	6
Bronchiectasis	14	12	2	0
Bronchogenic carcinoma	2	1	0	1
Chronic cough	57	38	13	8
Chronic laryngitis	1	1	0	0
Chronic sinusitis, otitis media or mastoiditis	21	12	5	7
Congenital pulmonary cysts	1	0	1	0
Deformed thorax	1	1	0	0
Emphysema	5	4	1	1
Frequent colds or sore throats	76	58	10	10
Hay fever	1	1	0	0
Pneumonia twice or more in the past	31	27	3	1
Pulmonary abscess	1	1	0	0
Recurrent hemoptysis	1	1	0	0
Septic pulmonary infarct	1	0	1	1
Tuberculosis, frequent pleurisy or pneumoconiosis	35	20	9	11
Alveolar abscesses	2	2	0	0
Peritonsillar and retropharyngeal abscess	1	0	1	1
Severe tonsillitis	2	2	0	0
Functional "heart" complaints (neurotic ?)	20	8	8	6
Cardiac				
Definite heart disease	163	89	69	30
Compensated	127	74	48	24
Decompensated	36	15	21	6
Auricular fibrillation (? cause)	16	5	10	8
Auricular flutter (? cause)	1	1	0	0
Arteriosclerotic (excluding hypertension)	57	37	19	4
Hypertensive (with or without arteriosclerosis)	50	29	20	7
Rheumatic (chronic)	23	12	10	9
Syphilitic	14	4	9	1
Congenital	1	1	0	0
Subacute bacterial endocarditis	1	0	1	1
Blood				
Anemia				
Secondary	4	2	1	2
Sickle cell	1	0	1	0
Leukemia				
Acute	1	0	1	0
Chronic	2	1	1	1
Dermatologic				
Burns	3	1	2	0
"Dermatitis and stomatitis"	1	0	1	0
Keratosis pilaris	1	1	0	0
Lichen planus	1	1	0	0
Pellagra	1	0	1	0
Psoriasis	1	1	0	0
Varicose ulcers	3	2	1	1
Gastrointestinal				
Appendicitis (no operation)	1	1	0	1
Bacillary dysentery	4	2	0	2
Inguinal hernia (no operation)	2	2	0	0
Peptic ulcer (no operation), 2 bleeding	3	3	0	0
Peritonitis (no operation)	1	0	1	1
Poisoning, saponated solution of cresol, ammonia, arsenic	3	1	1	1
Alcoholism				
Acute	21	11	8	2
Chronic	66	37	26	13
Ulcerative colitis (no operation)	1	1	0	0
Gynecologic and obstetric				
Bleeding uterine fibroids	1	1	0	0
Chronic pelvic inflammatory disease	3	2	1	1
Ovarian cyst (traumatic, twisted, ruptured)	3	1	2	2
Pregnancy				
Not interrupted before pneumonia	17	8	3	8
First trimester	5	4	0	1
Second trimester	7	3	2	3
Third trimester	5	1	1	4
Abortion during course of pneumonia	7	1	3	5
No abortion (or miscarriage or premature delivery)	10	7	0	3
Postpartum (before onset of pneumonia)	12	12	0	0

TABLE 1.—*Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed—Continued*

Concomitant Condition	Total No. of Patients	Outcome		
		Optimum	Death	Complication
Hepatic, biliary, and lienal (no operation)				
Banti's syndrome	2	1	1	0
Cirrhosis of liver	4	2	2	1
Gallbladder disease				
Acute	1	1	0	0
Chronic	6	2	4	1
Hepatomegaly	2	1	1	0
Jaundice				
Congenital hemolytic	1	1	0	0
Obstructive	2	0	2	0
Infectious (see other headings also)				
"Frequent night sweats"	1	0	1	0
Cellulitis, erysipelas	2	1	1	0
Furunculosis	3	2	1	0
Gonorrhea, acute	4	3	1	0
Malaria, Pl. falciparum	1	1	0	0
Pertussis	1	1	0	0
Rheumatic fever, acute	1	1	0	0
Staphylococcic septicemia	1	0	1	1
Syphilis, all evidences	104	61	35	15
Positive serologic reaction only, or treated	73	48	19	11
Syphilitic heart disease	14	4	9	1
Neurosyphilis	4	2	1	1
Other clinical evidences	13	7	6	2
Tuberculosis of femur	1	0	1	0
Varicella	1	0	1	1
Metabolic				
Diabetes mellitus	15	9	4	2
Mild	10	7	1	2
Severe	5	2	3	0
Hyperthyroidism	1	1	0	0
Hypothyroidism	3	2	1	1
Obesity	56	32	17	13
Recent loss of weight	34	26	5	4
Muscular, articular				
Muscular dystrophy	1	0	1	1
Arthritis (not pneumococcic)	4	1	3	1
Neoplastic—Carcinoma				
Breast	3	3	0	0
Bronchogenic	2	1	0	1
Cervix uteri	2	2	0	0
Pancreas (head)	1	0	1	0
Prostate	1	1	0	0
Skin	3	2	1	0
Trachea	1	1	0	0
Urinary bladder	1	0	1	0
Neurologic				
Aphasia	1	1	0	0
Cerebral thrombosis	1	0	1	1
Dementia praecox	1	1	0	0
Epilepsy	4	3	1	0
Neurosyphilis	4	2	1	1
Paranoia (congenital psychopathic inferior)	1	1	0	0
Skull fracture	1	0	1	0
Ophthalmologic				
Trachoma	1	1	0	0
Postoperative				
Oral	11	6	1	4
Abdominal				
Intestinal	3	1	2	0
Gastric	4	3	1	0
Appendical	12	11	1	0
Laparotomy	4	3	1	0
Cystostomy or cystotomy	5	2	3	1
Renal	5	5	0	0
Orthopedic	3	1	2	0
Miscellaneous	7	5	1	1
All postoperative	54	37	12	6
All abdominal				
Without peritonitis	16	14	2	0
With peritonitis	7	4	3	0

TABLE 1.—*Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed—Continued*

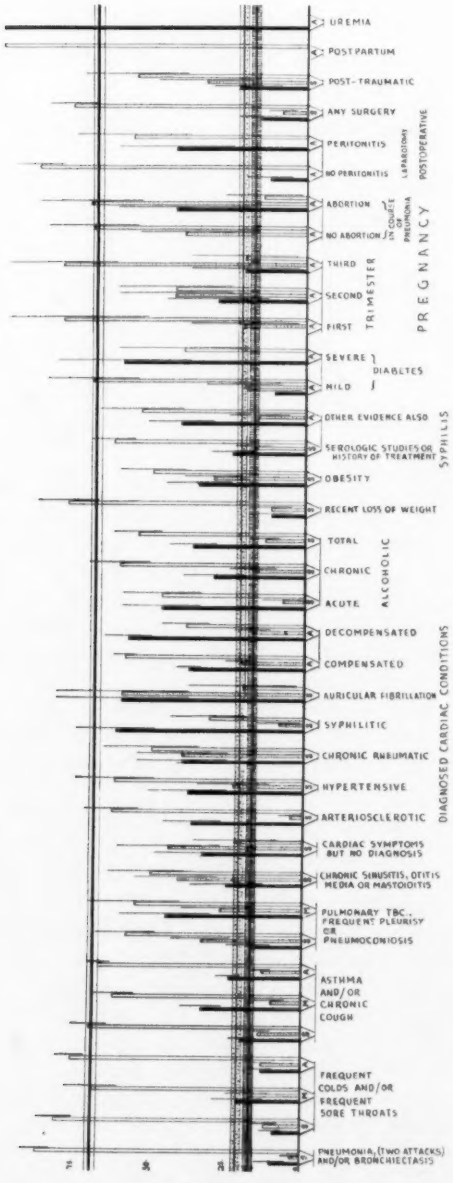
Concomitant Condition	Total No. of Patients	Outcome		
		Optimum	Death	Complication
Post-traumatic				
Chiefly confined to the thorax	15	9	4	2
Nonthoracic or generalized	7	3	4	1
Renal				
Undiagnosed urinary symptoms	9	6	3	1
Prostatism	4	3	1	0
Cystitis	2	0	2	0
Pyelitis	2	2	0	0
Pyelonephritis	3	0	3	1
Hydronephrosis (with cystitis)	1	0	1	0
Nephrosclerosis				
"Benign"	1	0	1	1
"Malignant"	1	0	1	0
Nephritis				
Acute glomerular	2	0	2	0
Subacute	1	0	0	1
Chronic	1	0	1	0
Uremia	5	0	5	0

* Patients with two or more concomitant conditions are listed once under each.

tended to be higher than among the control subjects but lower than among all patients with concomitant conditions. The monthly (not seasonal) incidence was virtually flat except for a sharp peak in midwinter. Serum was given to the same proportion of these patients as to those of the control group. There were fewer type II pneumococcus due to the infections and more due to the types with higher numbers than there were in the controls, but the differences carry little statistical weight. The improved outcome, the restricted pulmonary involvement and the presumably low incidence of bacteremia cannot be accounted for on the basis of type distribution and indicate that these patients may have had an increased resistance to extension and dissemination of the infection.

Twenty-four patients had pulmonary tuberculosis (the possibility of tuberculous pneumonia was thought to be ruled out), recurrent pleurisy or pneumoconiosis, without other known concomitant conditions. Their mortality was approximately the same as that of the controls, but their complication rate was suggestively elevated and their optimum outcome rate decreased. Types III and VII and the types designated by higher figures predominated. The ages were somewhat higher and the temperatures and leukocyte counts somewhat lower than among the controls. The mortality in the presence of additional concomitant conditions was rather definitely elevated. The presence of tuberculosis or pneumoconiosis or the recurrence of pleurisy in the past probably alters the "resistance" of the patient, making for a higher complication rate in pneumonia.

Patients complaining of "asthma" and of "chronic cough" were not distinguishable on the basis of outcome, and there were many such



CHART

(See legend on opposite page)

patients. One hundred and eleven patients presented one or both of these complaints, 69 being without other concomitant conditions. No significant difference existed between them and the controls, though the complication rate was lower, the mortality higher, the ages slightly higher, the fall and winter incidence increased, the leukocyte count and temperature a little lower and the incidence of types I and VIII increased at the expense of types II and III and group IV.

Complaints of frequent infections of the upper respiratory tract, described as colds, sore throats and the like, were made by 76 patients, and there was no other known abnormal condition in 47 of these. The outcome rates were suggestively better than those of the controls. Comparison of the 47 patients with the controls shows some increase in the incidence of types IV, VII and VIII and group IV as well as a decrease in that of types I, II and IX. Lobar lesions were less frequent and less extensive and blood cultures were negative for the 5 patients studied. (These differences carry little statistical weight.) It is possible that localized breaks in the patient's resistance are responsible for establishing the pneumonia, both in patients complaining of frequent infections of the upper respiratory tract and in those with bronchiectasis or recurrent pneumonia, but that the neighboring tissues often have an increased resistance and are able to prevent the local extension or wide dissemination of the organisms.

While only 12 patients presented chronic infections of the sinuses or the ears, without other concomitant conditions, they formed an interesting group. The marked elevation of the complication rate and depression of the optimum outcome rate carried little statistical weight. Although 7 of the 12 received serum, 3 died, 5 had complications and only 6 survived without complication.

The abnormalities of the respiratory system just mentioned may be arranged with respect to outcome, from best to worst: pneumonia twice or more, and/or bronchiectasis; frequent infections of the upper respiratory tract—colds, sore throats and others; "asthma" and/or "chronic

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LEGEND FOR CHART

Chart showing the percentage outcome (with their standard errors) for patients with certain concomitant conditions (vertical bars) and for all patients without known concomitant conditions (as horizontal lines reading from below upward indicating mortality, complication and optimum outcome rates). Optimum outcome is survival without complication. *S* represents patients with a single recognized condition (table 2); *M*, patients with multiple conditions, and *A*, all patients with the indicated condition (table 1). "Heart symptoms but no diagnosis" appears in the tables as "functional 'heart' complaints (neurotic?)"; "auricular fibrillation," signifies other heart disease not recognized. Arteriosclerotic-hypertensive heart disease is included in the chart with the "hypertensive" group. The terms "pregnancy" and "postpartum" designate the condition at the onset of pneumonia.

cough"; pulmonary tuberculosis, recurrent pleurisy or pneumoconiosis, and chronic sinusitis, chronic otitis media or chronic mastoiditis.

FUNCTIONAL CARDIAC COMPLAINTS

Nine patients complained of having had, without relation to the pneumonia, certain symptoms, such as palpitation, dyspnea, precordial pain and ankle edema, which are usually attributed to some abnormality of cardiac function; there were, however, no findings suggestive of car-

TABLE 2.—*Data on the More Common Concomitant Conditions in Patients Hav... With and "Witho...*

Concomitant Conditions in Patients with Only One Known Condition *	Total Number of Patients	Outcome (%)			Percentage Treated with Serum	According to Age				Sex; Percentage Male	
		Optimum	Death	Complication		1 to 19	20 to 39	40 to 59	60 and Over		
Pneumonia twice or more in the past and/or bronchiectasis	31	87	10	3	39	13	26	45	16	65	2
Frequent colds and/or sore throats	47	81	9	12	30	21	56	11	11	72	6
"Asthma" and/or chronic cough	69	70	19	14	48	9	48	33	10	57	4
Pulmonary tuberculosis, recurrent pleurisy, pneumoconiosis	24	58	17	33	38	0	29	59	13	62	0
Chronic paranasal or aural infection	12	50	25	41	58	8	66	25	0	25	8
Functional "heart" complaints (neurotic?)	9	22	33	44	56	0	22	33	44	44	0
Arteriosclerotic (excluding hypertension) heart disease	27	63	37	4	22	0	0	22	78	74	0
Hypertensive (with or without arteriosclerosis) heart disease	13	62	38	23	8	8	16	16	62	54	0
Chronic rheumatic heart disease	10	50	40	40	0	10	40	50	0	30	10
Syphilitic heart disease	13	31	62	8	15	0	8	31	62	69	0
Alcoholism: Acute	15	47	47	7	33	0	47	40	13	87	7
Chronic	23	61	30	17	39	0	52	43	4	83	13
Recent loss of weight	18	78	11	11	67	17	33	44	6	72	6
Obesity	20	50	35	30	40	5	25	40	30	35	5
Positive Wassermann reaction or therapy in past	46	63	24	17	28	4	50	39	7	76	7
Pregnancy	12	42	25	50	42	8	83	8	0	0	17
Postoperative	26	77	15	8	38	31	54	12	4	58	4
All patients in whom one or more concomitant conditions were											
Present	742	63	28	17	36	8	37	33	21	61	5
"Absent"	727	69	17	21	41	19	45	29	8	68	9

* Certain conditions were combined and considered the same if fundamentally allied, not differing in outcome a... often concurrent.

† Arabic figures indicate Cooper types; IV signifies group IV (in use until the latter part of 1936, when classification ... types 4 to 32 was introduced).

‡ "Atypical" includes only lesions definitely atypical ante mortem or possibly atypical lesions found atypical at autop...

diovascular disease. Under such circumstances it is not uncommon to pass over the complaints as evidences of neurosis in the patient or of overzealous prodding by the elicitor of the history. We were surprised to find that of the 9 patients only 2 survived without complication, 3 died and 4 had complications. In spite of the small number of patients, the differences between these rates and those of the controls carry considerable statistical weight. The extent of the change in outcome can be accounted for only with extreme difficulty on the basis of the higher age distribution or the greater number of infections of more than one

lobe. The outcome remained significantly poor, compared with that of the controls, when 11 patients were added who had other concomitant conditions as well. It is difficult to argue that the poor outcome was due to organic heart disease which was allowed to pass unrecognized, for the outcome was worse in these patients with undiagnosed symptoms than it was in patients with known but compensated cardiovascular disease. There may possibly be some underlying instability that accounts for these neurotic symptoms and for the poor outcome in pneumonia.

ily One Recognized Condition and Similar Data for All Patients
ncomitant Conditions

tribution (per Cent) of Patients														Results of Blood Culture		Distribution (per Cent) of Patients											
According to Type †								According to Pulmonary Involvement								According to Maximum Total Leukocyte Count §					According to Temp. (F.) on Admission ‖			According to Total Days Febrile ‖			
								All Cases																				
1	2	3	5	7	8	Other Cooper Types	Group IV	Per Cent Lobar	Per Cent Atypical	Lobar, per Cent 2 to 5 Lobes	Atypical,‡ per Cent Extensive	Sex: Percentage Male		Number of Patients	Number with Positive Cultures	No. of Patients	1 to 4	5 to 19	20 to 29	30 and Over	To 101	102 to 103	104 and Over	1 to 4	5 to 10	11 and Over	Questionable
6	3	13	0	10	6	19	26	74	26	26	0	6	0	22	5	68	18	9	12	64	23	23	45	32	0		
1	6	13	2	13	9	12	30	86	14	20	29	4	0	31	0	63	20	17	12	66	21	9	61	30	0		
0	4	7	6	9	12	15	16	92	8	35	25	14	3	43	0	67	26	7	19	61	20	12	47	41	0		
3	0	21	4	17	4	13	25	84	16	30	25	3	2	16	0	62	32	6	16	63	21	4	42	54	0		
0	8	8	0	0	8	8	25	84	16	39	50	2	0	7	0	72	14	14	8	50	42	0	67	33	0		
4	0	22	0	33	11	0	22	89	11	50	0	1	1	8	0	50	25	25	44	56	0	11	44	44	0		
3	0	15	4	4	4	52	11	40	60	18	12	2	0	12	0	75	17	8	41	55	4	7	56	34	4		
2	0	23	23	15	8	8	23	61	39	25	59	0	0	3	0	67	0	33	23	62	15	8	31	62	0		
0	10	30	0	0	10	30	20	60	40	50	0	2	1	8	0	75	25	0	40	50	10	10	50	40	0		
2	0	23	23	15	8	8	23	54	46	43	17	2	0	3	0	67	0	33	33	38	8	31	46	15	8		
7	7	7	7	7	0	41	27	93	7	22	100	3	0	13	0	85	15	0	20	67	13	27	40	27	7		
1	13	4	4	17	9	17	26	79	21	27	62	6	5	18	17	44	28	12	17	70	13	9	47	35	9		
3	6	6	0	39	6	17	6	89	11	26	0	2	0	16	0	56	31	13	28	40	33	17	56	28	0		
0	5	10	5	20	5	10	30	80	20	25	50	3	2	10	0	80	20	0	25	45	30	5	50	30	15		
2	7	7	11	7	4	11	39	92	8	36	25	6	1	27	0	59	34	7	20	52	28	2	56	40	2		
1	17	25	0	0	0	8	17	83	17	40	0	2	1	8	0	75	13	13	42	33	25	8	58	33	0		
0	4	12	4	8	4	58	12	58	42	34	10	1	0	13	0	54	46	0	38	34	27	15	62	23	0		
7	5	15	5	11	6	23	19	76	24	33	18	130	20	477	2	63	25	11	24	55	21	10	51	36	2		
7	9	11	3	10	3	12	22	91	9	33	20	112	13	462	1	60	27	13	17	49	34	9	53	34	2		

§ The "number of patients" signifies the number for whom total leukocyte count was made during acute illness: the distribution is according to the maximum recorded count, in thousands of cells.

‖ The maximum temperature during the first few hours in the hospital is given. By total days febrile is meant the number of days from onset to the last temperature above 99 F. before cure, death or the recognition of a complication.

CARDIOVASCULAR DISEASES

It is especially in the presence of cardiovascular diseases that the pneumonias are confusingly classified. If the heart is compensated, the pneumonia is generally assumed to be "primary" and the significance of the cardiac disease is minimized; if decompensation precedes the onset of pneumonia, the latter is usually called "secondary" or "terminal" and is often considered to be of relatively little importance, while if decompensation commences during the course of pneumonia, it is often looked on as a physiologic complication of pneumonia. Valid as that

classification may be, it offers considerable opportunity for misrepresentation.

Arteriosclerotic (nonhypertensive) heart disease was the only concomitant condition recognized in 27 patients, other conditions being noted in 30, making a total of 57. Comparison of patients having the single condition with the control subjects shows the optimum outcome rate unchanged, the mortality rate suggestively higher and the complication rate significantly lower (4 per cent). All the patients were over 40 years of age, and most were over 60. Controls of the same age had considerably higher death and complication rates than did the patients with arteriosclerosis, among whom there was a somewhat lower incidence of the more virulent types (half being types IX to XXXII and the other half I to VIII and group IV). More than half the lesions were atypical, and most of the lobar forms were limited to one lobe. The leukocyte count was somewhat lower, and the temperature on admission decidedly lower, than for the controls (of the same or of all ages). It is clear that the arteriosclerotic patients had an exceedingly low complication rate, as judged by any standard, and a mortality rate lower than for controls of the same age, while the pneumonias tended to be due to organisms designated by higher figures, to be atypical or limited in extent and to give rise to lower temperatures.

Hypertensive heart disease, with or without arteriosclerosis, was noted in 50 patients, in 13 of whom additional conditions were not recognized. The outcome among the 13 patients was apparently worse than that among the controls, but the difference carries little statistical weight. Only 1 of the patients received serum. Types III, V, VII and IX and group IV were represented. The age distribution and the temperature on admission were intermediate between those for the arteriosclerotic patients and those for the controls. In 12 of the 13 patients the disease developed during the winter "peak" months. Presence or absence of noncardiac conditions being disregarded, it was found that in the absence of decompensation the outcome was suggestively worse among the hypertensive than among the arteriosclerotic patients but that in the presence of decompensation there was no difference in the outcomes in the two groups.

Chronic rheumatic heart disease was diagnosed as occurring in 23 patients, 10 of whom had no other known concomitant condition. The outcome was suggestively worse than that among the controls. The 10 patients were characterized by a rather high incidence of extensive lobar lesions, a "normal" leukocyte count for half the studied patients, a relatively low temperature and a high incidence of women. These patients may be compared with the arteriosclerotic ones. The two groups had equal mortality rates, but the complication rate among the arteriosclerotic

patients was very suggestively lower. On the basis of the observed type distributions (control subjects being used as a measure), one would expect a complication rate of 16 per cent for the arteriosclerotic and 17 per cent for the rheumatic patients. The differences in age, sex and race were similarly inadquate to account for the observed difference in the complication rates. The effect of decompensation on the complication rate was virtually nil. Differences in the pulmonary involvements of the two groups would lead one to expect a 2 per cent difference in the complication rates. We are inclined to ascribe the difference to barriers against the spread of the pneumococci in the arteriosclerotic patients—probably on the basis of vascular and lymphatic sclerosis.

Syphilitic heart disease was the only concomitant condition present in 13 patients, in whom the outcome was definitely worse than in the controls (8 died, 1 had a complication and 4 survived without complication). The general characteristics of pneumonia in the presence of syphilitic heart disease were similar to those in the presence of hypertension, the apparently considerable difference in outcome carrying little statistical weight. In the patients with syphilis the low complication rate may have been a reflection of a very high mortality rate.[4] To what extent the poor outcome may have been due to the ravages of syphilis in other organs, such as the liver, cannot be estimated. It is interesting to compare patients with noncardiac syphilis with these patients. There were 73 patients on whom serologic studies gave positive results or who had a history of recent treatment, and in whom no other stigmas were found; 4 patients with neurosyphilis; 13 with additional evidence of syphilis (excluding cardiac and neurologic evidence), and the aforementioned patients with cardiac disease. For each of the groups the mortality was greater than for the controls, and the mortality rose from group to group when they were listed in the order just given. The incidence of complications was not impressive.

Auricular fibrillation is an extremely interesting condition in the patients with pneumonia. In the presence of organic heart disease it is usually looked on as a complication of that disease; in the absence of known heart disease it is considered as a "complication" of pneumonia (this has not been done in these papers), due either to embarrassed pulmonary circulation or (more probably) to profound "toxemia"—delirium cordis and delirium mentis being placed on the same basis. It is appar-

4. This argument rests on the contention that the course was abbreviated in about two thirds of the patients, so that insufficient time was available for the development of complications. If the patients had lived somewhat longer they might have died with rather than without complications or might have had complications but survived. (These variations in the outcome—fatality without complication, fatality with complication and survival with complicaton—may take place without affecting the optimum outcome rate.)

ent that proper classification demands knowledge of the ease with which the heart could be made to fibrillate in the absence of pneumonia and of the ease with which pneumonia could cause a normal heart to fibrillate. These questions are unanswerable, so far as we know, and we have therefore followed general practice by including patients with auricular fibrillation among those with the already mentioned cardiac conditions whenever possible. We present here a group of 16 patients without other known cardiac disease (additional, noncardiac concomitant conditions were present in 11). The disease was severe in these patients, and the outcome was significantly worse than in the controls. Only 31 per cent of the 16 patients survived without complication; 50 per cent had complications, and 63 per cent died, 44 per cent of the patients dying with complications.

In all, there were 163 patients with organic heart disease, in 36 of whom evidences of cardiac insufficiency were found. Decompensation was accompanied by a higher mortality and a lower optimum outcome rate than was compensation (the differences being rather significant), but there was no difference in the complication rates. The character of the underlying cardiac disease seems to have been of little importance in the presence of decompensation.

OTHER DISORDERS

Eighty-seven patients suffered from alcoholism (excluding patients described as minimal imbibers), in 38 of whom other concomitant conditions were not reported. Of the latter group, 23 had chronic alcoholism and 15 acute. The mortality rate was greater than in the controls, but the lowering of the complication rate carried little statistical weight. As regards the outcome, there was no significant difference between the patients with the acute and those with the chronic form of the disease. A short febrile course in those having acute alcoholism was due to early deaths. Pneumococci of types I, II, III and VII occurred in 57 per cent of the controls, in 48 per cent of all patients with concomitant conditions, in 43 per cent of those with chronic alcoholism and in 28 per cent of those with acute alcoholism.

A recent loss of weight was noted in the histories of 34 patients, 18 of whom were without other abnormal conditions. The observed improvement in outcome carried no statistical weight (the odds being about 5 to 1 that the difference was not due solely to chance). Of 56 patients showing obesity, 36 had other conditions as well. Most of the remaining 20 patients were women and over 40 years old; their mortality was rather significantly elevated, but their complication rate was the same as that of the controls. Obesity was not in these patients a particularly grave concomitant condition.

Though there were few patients with diabetes mellitus, they presented interesting findings. In the absence of coma or excessively high blood sugar levels (10 patients) the outcome was no worse than in the controls, but among the 5 patients with severe diabetes the mortality was suggestively higher than among either the patients with mild disease or the controls. The pneumonia tended to be atypical and not particularly extensive. All the patients were febrile ten days or less before cure, death or recognition of complications, there being no other group with such a short course.

Pneumonia was superimposed on pregnancy in 17 patients, other conditions being "absent" in 12. Abortion (including miscarriage and premature delivery) occurred during the course of the pneumonia in 7 of the 17. In the absence of abortion death did not occur, but a third of the patients had complications (of the pneumonia). When abortion occurred during the pneumonia, the mortality and the complication rate rose to high levels and the optimum outcome rate fell to a minimum. The outcome became progressively worse with increasing duration of the pregnancy, but this reflected an increasing incidence of abortion. The general elevation of the complication rate cannot be ascribed entirely to the type distribution. It is probable that the occurrence of abortion was an indication of the severity of the pneumonia. We feel that it is possible that pregnant women are unusually resistant to pneumonia; that when they do become infected the disease is frequently due to one of the more virulent types of pneumococcus; that if abortion can be avoided the patients are more than usually able to cope with the "toxemia" of pneumonia and to survive, but are not particularly resistant to the development of complications; that the chances of abortion increase with the duration of the pregnancy, and that if abortion does occur during the pneumonia the mortality and the complication rate rise to high levels. In suggesting that the resistance is increased, we have considered further evidence presented by 12 postpartum patients in whom pneumonia developed: all survived without complications.

Post-traumatic or postoperative pneumonia was found in 80 patients. Patients in whom pneumonia developed after general trauma (as from automobile accidents) had a suggestively higher mortality rate than the controls. The outcome in all patients with postoperative pneumonia was not statistically different from that in the controls. No complications occurred in 24 patients with pneumonia following laparotomy, but in the presence of peritonitis the mortality was elevated.

Eighteen patients had various forms of disease of the liver or biliary tract; 58 per cent of them died (a highly suggestive increase in mortality over that of the controls). Some form of renal disease (excluding prostatism) was diagnosed as present in 13 patients: 1 of the 3 who

survived (subacute nephritis) and 2 of the 10 who died had complications (uremia occurred in 5 of those who died). These concomitant diseases are thought to have been present before the onset of the pneumonia. The deplorable outcomes may indicate the importance of the liver and kidneys in the natural defenses against pneumonia.

COMPARISON OF THE TWO GROUPS OF SUBJECTS

The 742 patients with concomitant conditions may be compared with the 727 controls. In the former group there was an impaired outcome; a higher death rate, a lower optimum outcome rate and a suggestively lower complication rate. The incidence of types I and II was decidedly diminished, while the incidence of types III, IV, V, VIII and those designated by higher figures was slightly increased. The pulmonary involvement was much more often atypical but was no less extensive. The temperature on admission tended to be somewhat lower, but the febrile course was not abbreviated. The patients were definitely older, on the average; the sexes were more equally represented, and there were fewer Mexicans (owing, perhaps, to difficulties in eliciting complaints pointing to concomitant conditions). Bacteremia was more frequently found when looked for, but there was no difference in the leukocyte count.

SUMMARY AND CONCLUSIONS

The records of 1,469 patients with pneumococcic pneumonia were examined in an effort to learn the effect of the presence of certain concomitant conditions on the outcome and character of the pneumonia. All observed conditions are noted, the most frequent or important being discussed.

Mary C. Moore and Josephine Abraham lent valuable assistance in the analysis of data.

MULTIPLE PRIMARY MALIGNANT LESIONS OF THE LARGE BOWEL

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Multiple primary malignant lesions of the large intestine have been reported occasionally. A number of factors have made this study seem timely: (1) the bearing that this syndrome may have on the problem of cancer in general; (2) the great importance that these multiple tumors may possess in respect to the prognosis for patients who have malignant lesions; (3) the relative paucity of attention that multiple malignant lesions of the large bowel have received, and (4) the relationship that polyps bear to the pathogenesis of malignant lesions of the large bowel.

Ewing,[1] Hanlon[2] and Orr[3] stated the belief that multiple primary malignant lesions are merely coincidental occurrences. Warren and Gates[4] have not expressed the same opinion, and a study of the cases reported in the present paper would draw us also away from such an opinion. Maud Slye[5] was able to demonstrate that "in mice resistant by heredity, irritations and traumas incident to life in this laboratory have never been able to induce cancer, while in mice susceptible by heredity to only one location of cancer, irritations or stimulations applied to other parts of the body have to date failed to induce neoplasms in these insusceptible tissues." Her ability to breed into mice as well as to breed out of mice the tendency, not alone toward malignant disease in general, but also toward specifically localized tumors, seems to indicate that some

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1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 37.

2. Hanlon, F. R.: Multiple Primary Carcinomas, Am. J. Cancer **15**:2001-2012 (July) 1931.

3. Orr, J. W.: Multiple Malignant Neoplasms, J. Path. & Bact. **33**:283-290 (April) 1930.

4. Warren, S., and Gates, O.: Multiple Primary Malignant Tumors: A Survey of the Literature and a Statistical Study, Am. J. Cancer **16**:1358-1414 (Nov.) 1932.

5. Slye, M.: The Relation of Heredity to the Occurrence of Cancer, Radiology **29**:406-433 (Oct.) 1937.

inheritable biologic factor influences the destiny of a group of tissues. There are many clinical observations at hand which gave support to Slye's work.

It has been noted that multiple cancers occur in various tissues of the same person and at various sites in the same organ, such as the large intestine. Furthermore, a tendency to such occurrences has been encountered among various members of families through several generations.

In the past, the decision as to whether two lesions were independent of one another rested on Billroth's postulates, namely: 1. The two growths must show distinct histologic differences. 2. Each growth must spring from its parent epithelium. 3. Each growth must be held responsible for its own metastatic lesions. Mercanton [6] added still another condition when he pronounced that the independence of the growths from one another is assured if the patient remains free from disease after the removal of the second lesion.

The criteria suggested by Warren and Gates are more applicable to lesions in the same organ, and the fulfilment of certain conditions was a prerequisite to the inclusion of multiple lesions in their series. These conditions are: (1) Each tumor must be malignant; (2) each growth must be distinct, and (3) one lesion cannot be a metastatic implant from the other.

In the past, transplantation from one site in the bowel to another was thought to explain the occurrence of more than one lesion. Transplantation of carcinoma in the large bowel from one site to another is extremely rare. Transplantation by way of the lumen would fail entirely to explain those cases in which the proximal growth is smaller than and far separated from the distal growth. Furthermore, the mucus secreted in the large bowel, the peristaltic activity of the bowel and the force of the fecal stream probably would not allow the cells cast off from one growth to grow at a distal site. Implantation of cancer cells no doubt occurs at some sites, notably in cases of Krukenberg's tumors of the ovary, but this is not the correct explanation for the multiple growths in the large bowel. Robertson,[7] after an extensive experience, has remarked that carcinomatous transplantation in the large intestine must be extremely rare.

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6. Mercanton, F., cited by Miller, R. T., Jr.: Multiple Primary Malignant Foci in Cancer of the Colon, Ann. Surg. **80**:456-472 (Sept.) 1924.

7. Robertson, H. E.: (*a*) Personal communication to the authors; (*b*) Polyps of the Colon and Their Possible Significance, Bull. Am. Soc. Control Cancer **16**: 6-7 (Feb.) 1934.

We have gathered 23 cases from the records of the Mayo Clinic since the report by Rankin and one of us (Bargen [8]) was made and have divided them into two groups: (1) those in which multiple cancers occur simultaneously (synchronous) and (2) those in which multiple cancers occur at different times (metachronous). We have excluded from this series of cases instances of multiple polyps of low grades of malignancy and of single lesions that grossly were undoubtedly carcinomatous and that were associated with single polyps of a low grade of malignancy. Such cases may belong in a group of cases of multiple primary neoplasms, but the divergence of opinion at this time precludes such a classification. The single or multiple occurrence of polyps with cancer of the large intestine is common. If these polyps are precancerous lesions, why is there a great variation between the incidence of polyps and that of cancer? It would seem that part of this discrepancy can be accounted for by the fact that many patients who have polyps in the large bowel die from other causes before the polyps have had time or sufficient stimulation to become malignant. The interpretation of the microscopic structure of polyps of the "borderline" variety is dependent on the variables of past training and personal convictions. Polyps labeled adenocarcinoma of grade 1 may well be termed "benign" by some. Whether any particular growth of this description will eventuate in carcinoma can only be conjectured. Too many unknown and unpredictable elements are involved in such a question. It is certain, however, that not all polyps will become liabilities to their hosts.

REPORT OF CASES

GROUP I

CASE 1.—A man aged 58 years came to the clinic on Sept. 16, 1931; he complained of pain in the rectum and bloody stools of six months' duration. Three months before admission morning diarrhea had begun, together with tenesmus and bloody stools.

Examination, disclosed an annular carcinoma in the proximal half of the rectum. At operation, colostomy was performed and a second lesion was found in the sigmoid flexure. The pathologic report was colloid adenocarcinoma of the rectum of grade 3, measuring 9 by 6 by 2.5 cm., and annular adenocarcinoma of the sigmoid flexure of grade 2, measuring 6 by 5 by 1.5 cm. The lymph nodes were not involved.

CASE 2.—A man aged 54 years came to the clinic on Aug. 20, 1937; he complained of a sensation of pressure in the lower part of the abdomen, relieved by voiding. This distress gradually became more severe and was associated with malaise and some nausea. About one month before his arrival at the clinic, this pain became localized in the left lower abdominal quadrant and a questionable mass appeared in that region. During the three weeks preceding admission, the patient had lost 16 pounds (7.3 Kg.).

8. Bargen, J. A., and Rankin, F. W.: Multiple Carcinomata of the Large Intestine, Ann. Surg. **91**:583-593 (April) 1930.

Examination revealed a large, firm, tender mass in the left lower abdominal quadrant. Roentgenologic examination revealed changes suggestive of a perforating carcinoma of the descending colon. Pathologically there were two lesions: The more proximal lesion was adenocarcinoma, grade 2, which measured 2.5 by 2 by 1 cm.; the more distal lesion was polypoid adenocarcinoma, grade 3, which measured 3 by 3 by 1 cm. The lymph nodes were not involved.

CASE 3.—A man aged 55 years came to the clinic on Dec. 12, 1929. For eight years this patient had noted a passage of blood with hard stools. During the eight weeks that preceded his admission there had been a frequent desire to defecate, often resulting only in the passage of flatus and a little blood. The patient remarked that he had felt "as though he were blocked." The caliber of the stools had diminished recently and the patient had lost about 10 pounds (4.5 Kg.).

Examination disclosed two lesions in the rectum. The pathologic report was adenocarcinoma of the lower part of the rectum, grade 2, measuring 3 by 3 by 1.5 cm., and polypoid adenocarcinoma of the upper part of the rectum, grade 2, measuring 2 by 2 by 1 cm.

CASE 4.—A woman aged 43 years came to the clinic in January 1933, with a history of having noted a little blood in the stools for one year. During the six months that preceded her admission, she had been severely constipated and had been aware of an aching soreness in the rectum.

Examination revealed a large cauliflower-like lesion on the posterior rectal wall. The pathologic report was polypoid, ulcerating adenocarcinoma of the rectum, grade 2, measuring 6 by 5 by 2 cm., with extensive involvement of a vessel, probably a vein, and surrounding connective tissue. A second primary growth was found 7 cm. proximal to the lesion, adenocarcinoma, grade 2, with shallow ulceration.

CASE 5.—A man aged 45 years came to the clinic on Dec. 7, 1936. For three years preceding his admission the patient had suffered from recurring episodes of diarrhea, with the passage of four to six watery stools each day for three or four days. Between these episodes of diarrhea, the bowel habits were entirely normal. For six months prior to aumission the patient had had a sensation of not completely emptying the rectum, and in addition to one or two normal stools daily he would pass three or four bloody, mucoid rectal discharges.

Examination disclosed a lesion in the rectum. At operation, a second growth was found in the descending colon. The pathologic report was ulcerating adenocarcinoma of the descending colon, grade 2, measuring 6 by 5 by 1 cm. The lesion in the rectum was an adenocarcinoma of grade 1. In addition, this patient also had an epithelioma of the penis.

CASE 6.—A man aged 45 years came to the clinic in 1914; he complained of intercostal neuralgia. For some time he had passed a little mucus in the stools, but the bowel movements otherwise had been normal.

Examination revealed a polyp 12 cm. from the anal margin without ulceration. The patient was urged to have this growth removed but he refused. He returned on Oct. 16, 1930 and stated that for one year prior to this date an already chronic constipation had become increasingly severe and in addition that he had passed a little blood with the stools. For two months preceding his admission there had been a progressive loss of strength and a loss of 18 pounds (8.2 Kg.). In August 1930 a colostomy had been performed, elsewhere. Since that time, bleeding had increased, and the patient passed four to eight bloody rectal discharges daily.

Examination revealed a large annular mass in the middle third of the rectum, with marked fixation and obstruction. Just distal to the growth, there was another flat malignant lesion. The pathologic report was adenocarcinoma of the rectum, grade 2, measuring 8 by 6 by 3 cm.; 2 cm. distally a second lesion was found, adenocarcinoma, grade 3, measuring 1.5 by 1 by 5 cm. The lymph nodes were not involved.

CASE 7.—A man aged 70 years came to the clinic on Aug. 9, 1937 and related a history of having five to nine unformed bowel movements daily for three years. Blood had not been present in any of the rectal discharges.

Examination revealed a polypoid lesion on the anterior rectal wall. Roentgenologic examination disclosed an annular lesion in the descending colon at the level of the iliac crest. The pathologic report was ulcerating adenocarcinoma of the descending colon, grade 2, measuring 4 by 3 by 1 cm., and adenocarcinoma of the rectum, grade 1, measuring 7 by 5 by 2 cm. Lymph nodes were not involved.

CASE 8.—A man aged 59 years came to the clinic on Aug. 12, 1937; he related a history of having passed bloody, mucoid rectal discharges for three years and at times only bloody mucus. For two years preceding his admission, the patient had noted a diminishing caliber of the stools; they gradually became soft, then watery and finally more frequent—five to seven stools daily.

Examination revealed a mass in the rectum; the sigmoid flexure was firm, tender and irregular. Proctoscopic examination revealed an annular, ulcerated lesion 9 cm. from the anus; it involved the proximal third of the rectum and caused severe obstruction and fixation. The pathologic report was adenocarcinoma of the rectum, grade 3, measuring 3 by 3 cm.; distal to the other lesion was an adenocarcinoma, grade 2, measuring 7 by 7 by 3 cm. Lymph nodes were not involved. This patient also had a squamous cell epithelioma of the urinary bladder, grade 3.

CASE 9.—A woman aged 41 years came to the clinic on Nov. 15, 1937 and related a history of rectal urgency and bleeding of one year's duration. During the six months preceding her admission, there had been bloody mucoid discharges and the passage of two or three formed stools daily.

Examination revealed a lesion in the sigmoid flexure. Just above the anus on the anterior rectal wall was a second lesion, 3 to 4 cm. long. The pathologic report was annular ulcerating carcinoma of the sigmoid flexure, grade 2, measuring 5 by 5 by 3 cm., and adenocarcinoma of the distal part of the rectum, grade 1. The lymph nodes were not involved.

CASE 10.—A woman aged 50 years came to the clinic on Sept. 15, 1937. Since 1903, this patient had suffered from sour stomach and acid eructations. Three years preceding her admission these symptoms became aggravated. There was a feeling of fulness after meals and occasional vomiting, and at that time the first attack of dull pain occurred in the right upper abdominal quadrant. Since then, there had been several similar attacks, usually accompanied by nausea and vomiting. Six months before admission, the patient had begun to pass two watery stools daily, although previous bowel habits had always tended toward constipation. During the six months before admission to the clinic, there had been a loss of 30 to 40 pounds (13.6 to 18.1 Kg.). Examination revealed a filling defect in the cecum and ascending colon and a small "polyp" on the right rectal wall. The pathologic report was ulcerating adenocarcinoma of the cecum, grade 2, measuring 6 by 5 by 2 cm., and polypoid adenocarcinoma of the ascending colon, grade 2,

measuring 3 by 4 by 2 cm. These lesions were 3 cm. apart. There was some involvement of lymph nodes.

CASE 11.—A woman aged 56 years came to the clinic on Sept. 8, 1937. This patient had been well until January 1936, when she had suffered from an attack of intestinal obstruction. Since July 1936 there had been intermittent attacks of a low grade of obstruction, with only occasional rectal discharges. Examination revealed the obstruction to be in the sigmoid flexure. The pathologic report was ulcerating, perforating carcinoma of the sigmoid flexure, grade 2, measuring 4 by 3 by 3 cm.; ulcerating adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 3 cm., and ulcerating, perforating adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 2 cm. There was some involvement of lymph nodes.

CASE 12.—A woman aged 59 years came to the clinic on Jan. 31, 1935, complaining of general weakness and anemia for six months. During this time, there had been generalized abdominal pains resembling the pains of labor. During the four weeks preceding admission, there had been some rectal urgency and the passage of flatus or bloody mucus. Also, there had been slight pain in the rectum accompanying bowel movements.

Examination revealed a lesion in the sigmoid flexure and another in the ascending colon. The pathologic report was papillary adenocarcinoma of the sigmoid flexure, grade 2. Involvement of lymph nodes was not found. The patient died after anterior resection of the sigmoid flexure was performed. The presence of the lesion of the ascending colon was confirmed.

CASE 13.—A woman aged 59 years came to the clinic on Nov. 29, 1937; she related a history of having suffered from gas pains and the daily passage of one or two mushy stools without blood.

Examination revealed a defect in the transverse colon. At exploratory operation colloid adenocarcinoma of the cecum, grade 1, measuring 6 by 5 by 2 cm., with serosal involvement, and ulcerating colloid adenocarcinoma of the transverse colon, grade 1, measuring 8.5 by 5 by 1 cm., were found. The mucosa between the two lesions was studded with adenomatous polyps 1 to 2 cm. in diameter, many of which were adenocarcinoma of grade 1.

CASE 14.—A woman aged 39 years came to the clinic on Dec. 3, 1936; she related a history of having had for ten months prior to admission recurring constipation and diarrhea with the passage of eighteen to twenty bloody, mucoid stools daily. Such episodes were accompanied by abdominal cramps and distention, and the associated vomiting persisted for seven to fourteen days. One month preceding her admission, the patient had suffered from an attack of severe abdominal pain with almost persistent vomiting and a failure to pass either flatus or stool for twenty-four hours. During the three months before her arrival at the clinic, the patient had noticed an inability to retain more than 8 ounces (240 cc.) of fluid in the rectum.

Examination disclosed a large annular ulcerating lesion of the rectosigmoid, with severe obstruction. Below the lesion were a number of sessile polyps. Because of the severe obstruction, exploration was not attempted at the time that colostomy was performed. Three weeks postoperatively, a cystic tumor was noted in the right lower abdominal quadrant. This was accompanied by recurring signs of obstruction. At the time of the second operation, a mass was found in the transverse colon just distal to the hepatic flexure. This mass was the size of an orange and was producing almost complete obstruction. It was removed. The pathologic

report was colloid adenocarcinoma of the hepatic flexure, grade 3. Glandular involvement was not noted. At the time of the combined abdominoperineal resection, an adenocarcinoma, grade 1, of the proximal part of the rectum was removed; it measured 3 by 2 by 1.5 cm. Distal to this there was a colloid adenocarcinoma, grade 2, that measured 6 by 5 by 1.5 cm. In the rectum and sigmoid flexure there also were a number of adenomatous polyps, pedunculated and sessile, ranging in diameter from 1 mm. to 1 cm.

CASE 15.—A woman aged 48 years came to the clinic on Aug. 20, 1934. She had been well until the winter of 1933-1934, when she first experienced abdominal discomfort accompanying bowel movements. In the spring she began having five to six bloody mucoid stools daily and considerable rectal pain. The patient had lost about 10 pounds (4.5 Kg.).

Examination revealed an indurated mass high in the rectum. At operation colostomy was performed and a second mass was discovered in the sigmoid flexure. The pathologic report on the resected lesion of the sigmoid flexure was colloid adenocarcinoma, grade 2, with involvement of lymph nodes, grade 2. The lesion in the rectum was adenocarcinoma, grade 2.

CASE 16.—A man aged 55 years came to the clinic on May 27, 1926; he complained of colicky pains in the hypogastrium, mostly on the left side and usually more severe about twenty minutes after meals. This distress was relieved by a bowel movement. During the six months preceding the onset of these symptoms constipation had increased, and during the three months preceding his admission to the clinic the caliber of his stools had diminished. At no time had there been blood, pus or mucus.

Examination revealed an elongated, tender mass in the left lower abdominal quadrant. At operation a tumor was found in the sigmoid flexure. The pathologic diagnosis was adenocarcinoma of the sigmoid flexure, measuring 6 by 4 by 1.5 cm. Lymph nodes were not involved. There was also a polypoid soft growth in the posterior rectal wall. The patient was urged to have this removed, but refused. On Sept. 20, 1933 he was readmitted to the clinic because of a recent increase in the amount of mucous discharge from the rectum and occasional, slight, bloody discharge. There had also been a bearing down feeling and a sense of fulness in the rectum. Examinations revealed a large polypoid mass on the right posterior rectal wall. The pathologic report was polypoid adenocarcinoma of the rectum, grade 1, measuring 4 by 6 by 4 cm. The lymph nodes were not involved.

GROUP II

CASE 17.—A woman aged 44 years came to the clinic on June 17, 1933. This patient had had a resection of the transverse colon performed elsewhere in 1921 for carcinoma. She had remained well until six months before her admission, when general weakness developed. Two months preceding admission a mass was discovered in the right lower abdominal quadrant, and since that time there had been some diarrhea without blood. In the six months preceding admission the patient had lost 45 pounds (20.4 Kg.).

Examination revealed filling defects in the cecum and ascending colon. Surgical resection was undertaken. The pathologic report was colloid adenocarcinoma of the ascending colon, grade 2, measuring 5 by 5 cm., and colloid adenocarcinoma of the cecum, grade 2, measuring 6 by 6 cm. The lymph nodes were involved.

CASE 18.—A man aged 46 years came to the clinic in November 1901 and was operated on for carcinoma of the cecum. He returned, at the age of 78, on Feb. 11,

1933. Nine months preceding his second admission, he had experienced sharp pains over the entire abdomen, with a sense of fulness after meals, increasing constipation and occasional rectal bleeding. One week preceding admission, signs of comparatively severe intestinal obstruction had developed. A resection of the sigmoid flexure was performed, and the pathologic report on the resected specimen was annular adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 1 cm. The lymph nodes were not involved.

CASE 19.— A man aged 50 years came to the clinic on Sept. 7, 1933. Three years preceding his admission, a diagnosis of peptic ulcer was made because of epigastric distress. Beginning two years before admission, there had been abdominal pain accompanied by vomiting one hour after meals and persisting three or four hours, occurring every four or five weeks. These symptoms had increased in frequency and severity. Colostomy was performed elsewhere for obstruction.

Examination at the clinic revealed a lesion in the cecum. The pathologic report on the resected specimen was annular, ulcerating adenocarcinoma of the cecum, grade 4, measuring 9 by 7 by 4 cm.

This patient returned to the clinic on Feb. 18, 1938 and stated that he had passed four or five loose stools daily and had had rectal burning for five months. Previous to the onset of these symptoms he had been entirely well. There had been some rectal bleeding, less during the two months preceding admission.

Examination revealed an annular lesion beginning at the dentate margin. The pathologic report on the resected specimen was annular, ulcerating adenocarcinoma, grade 2, measuring 5 by 5 by 2 cm. Just lateral to the growth was a pedunculated adenocarcinoma, grade 1, measuring 2 by 2 by 1 cm. The lymph nodes were not involved.

CASE 20.—A man aged 49 years came to the clinic on Aug. 26, 1935. Two years before his admission, there had been diarrhea for one month. For one year prior to admission to the clinic, there had been gnawing pain in the abdomen associated with the return of diarrhea, which was persistent and progressive. For five or six weeks before admission, each day he had passed eight to ten mushy stools free of blood. During this interval there had been a loss of 10 pounds (4.5 Kg.).

Examination revealed a lesion in the region of the rectosigmoid, and at the time of surgical exploration a large mass also was discovered in the cecum. The pathologic report on the resected specimens was adenocarcinoma of the cecum, grade 3, measuring 7 by 8 by 3 cm., without involvement of lymph nodes, and also ulcerated, pedunculated adenocarcinoma of the sigmoid flexure, grade 3, measuring 6 by 4 cm.

The patient returned on Nov. 17, 1937; he stated that he had been well for one year, and then had become aware of a heavy feeling in the lower part of the abdomen and had required liquid petrolatum to insure bowel movements. Examination revealed a lesion in the descending colon. The pathologic report on the resected specimen was mucoid adenocarcinoma of the descending colon, grade 3, measuring 8 by 5 by 2 cm., with extension to the serosa. The lymph nodes were not involved.

CASE 21.—A man aged 55 years came to the clinic on Nov. 29, 1933; he related a history of progressive weakness and loss of weight during the preceding three months. During the six weeks prior to his admission, there had been pain and tenderness in the right lower abdominal quadrant, as well as some generalized abdominal cramps and gradually increasing constipation. During the past year the

patient had been aware of a mass in the right lower abdominal quadrant. Examination revealed a lesion in the ascending colon. The pathologic report on the resected specimen was ulcerating, colloid adenocarcinoma of the ascending colon, grade 2, measuring 12 by 7 by 3 cm., with peritoneal involvement.

The patient returned on July 19, 1938; he stated that he had been well until one year prior to his second admission. Then constipation had developed; aching pains in the rectum and testes had occurred, mostly at night. Each day he had passed four to ten mushy stools, which were often bloody, and occasionally he had been awakened three to four times at night with the desire to defecate. Bleeding had been more severe in the three months preceding admission.

Examination revealed a huge, fixed, inoperable lesion in the lower part of the rectum. The pathologic report was colloid adenocarcinoma, grade 1.

CASE 22.—A man aged 40 years came to the clinic on April 14, 1926; he related a history of easy fatigue, increasing constipation and daily use of laxatives for two years preceding admission. Examination revealed a lesion in the cecum. The pathologic report on the excised specimen was colloid adenocarcinoma, grade 1, measuring 8 by 2 by 2 cm.

The patient returned in May 1927 and appeared to be in good health. He returned again on June 6, 1936, at which time he complained of abdominal cramps and two to six loose stools daily for one year. There had been no bleeding.

Examination revealed a lesion in the descending colon as well as a small sessile polyp in the rectum. The pathologic report on the resected specimen was adenocarcinoma of the descending colon, grade 2, without involvement of lymph nodes.

CASE 23.—A woman aged 62 years came to the clinic on June 10, 1931. She had been perfectly well until six months before her arrival at the clinic. Then there developed tenesmus and rectal urgency, together with the passage of gas and blood. She had become increasingly constipated. Examination revealed a lesion in the lower third of the rectum. The pathologic report on the resected specimen was adenocarcinoma of the posterior rectal wall, grade 3, measuring 4 by 6 by 6 cm. The lymph nodes were not involved.

The patient returned to the clinic on July 2, 1934; she related a history of increasing cramps in the midabdomen, aggravated by meals. The previously performed colostomy was functioning well. Roentgenologic examination revealed a filling defect in the cecum. The pathologic report on the resected specimen was annular ulcerating papillary adenocarcinoma of the cecum, grade 3, measuring 9 by 7 by 7 cm., with multiple small polyps and diverticula proximal and distal to the growth. The lymph nodes were not involved.

COMMENT

In some of the cases cited, such as case 6, the possibility of implantation might be thought of, but in this case and in other similar cases, careful pathologic study failed to reveal any connection in the wall or lining of the bowel between the distal and the proximal growth. Both arose at points distant from one another in the rectal mucosa.

A critical analysis of some cases, such as cases 12 and 13, might raise the question: Why is not one of the lesions an extension from the other? However, even if involvement of lymph nodes was found,

evidence of any connection between the two lesions could not be ascertained. They were individual lesions arising in close proximity from different sites in the mucosa of the bowel.

It is probably a fact that in many instances multiple independent lesions in the bowel are not recognized. The importance to the patient of the physician's failure to exclude the possibility of other lesions is apparent. It is interesting to speculate on the proportion of poor results after operation for cancer that are attributable to synchronous or metachronous lesions, unsuspected and therefore undiscovered. Curability by operative means will improve, therefore, only as diagnoses are made earlier and are thorough. That is a responsibility of the clinician, and it is a great one indeed. When a diagnosis of hemorrhoids is made only after all other possible causes of bleeding from the bowel have been excluded, when digital and proctoscopic examinations of the rectum and the sigmoid flexure become routine procedures, the percentage of cases of cancer of the large bowel in which the condition is inoperable when first seen by the surgeon will diminish.

Brindley,[9] in a recent consideration of this subject, concluded that a patient with cancer is more likely to have a second malignant lesion develop than the subject who is free of cancer. The implication is clear: Once a patient has become the victim of a malignant lesion in the large intestine, he should be instructed adequately to watch for warning signs of recurring trouble. According to our experience many patients after having had a cancer of the colon removed tend to assume erroneously that they are from that time forth immune to a similar morbid process.

That the explanation of the pathogenesis of polyps may explain also the origin of cancer of the colon seems more than likely. Robertson put it nicely when he said: "The usual growth of cells is so well regulated that parasitic masses do not occur. Cancer, then, does not come from 'stimulation of growth' as is so frequently asserted but because the normal mechanism for governing orderly growth is disturbed." That there must be a force which governs normal growth becomes almost apparent when one observes the fineness of adjustment in the healing of wounds. The repair of injured tissue progresses at a rapid rate, but as needed repair approaches completion the rate of proliferation of tissue becomes slowed and finally is reestablished at the normal rate. Proliferation is an inherent characteristic of all tissues. Whether the cancers reported in this paper originated in polyps remains unproved. That polyps play a role in the genesis of some cancers cannot be denied. These facts emphasize the importance of a careful examination of the entire large intestine when cancer is found at any point in it.

9. Brindley, G. V.: Multiple Primary Malignancies of the Large Intestine, South. M. J. **31**:355-362 (April) 1938.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1940

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Several important books have appeared this year in the field of neurology and psychiatry. In the first place stands Wilson's "Neurology,"[1] published posthumously and edited by Wilson's great friend Ninian Bruce. The book is complete, scholarly and well written. It supplants the old Oppenheim, and to say that is high praise indeed. As a book of reference it is indispensable, but it is not a handbook for students.

Another important book by an English author is the "Selected Writings of Sir Charles Sherrington," edited by Denny-Brown.[2] The published papers of Sir Charles are scattered through so many journals and over such a long period of time that many of them are difficult to find. They contain a mass of systematic observation and faithful record that gives a classic example of the scientific method and makes a monumental contribution to the literature of the nervous system. It is therefore a great boon to any neurologic library to have this book of sources with well chosen reprints and abstracts, which include such important observations as the original description of the spinal and of the decerebrate animal, the experimental isolation of skin and muscle segmentation, the proof for muscle sensibility, the motor representation in the primate cortex and the fundamental work on reciprocal innervation and postural reflexes. Any one of these contributions is enough to have made a physiologist great.

A different production in every way is "The Varieties of Human Physique," by Sheldon and his co-workers.[3] Here is the work of a trained specialist bringing to medicine the results of labors in anthropology and mathematics. Many earlier workers had classified persons into types, from Hippocrates, who divided mankind into the *habitus*

1. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940.

2. Denny-Brown, D.: Selected Writings of Sir Charles Sherrington, New York, Paul B. Hoeber, Inc., 1940.

3. Sheldon, W. H.; Stevens, S. S., and Tucker, W. B.: The Varieties of Human Physique, New York, Harper & Bros., 1940.

appoplecticus and the *habitus phthisicus,* through Walker, in 1852, with his "nutritive beauty" (Venus), "locomotive beauty" (Diana) and "mental beauty" (Minerva), to Kretschmer, in 1925, with his widely accepted "pyknic, athletic and asthenic" types. All had more or less definite ideas that these body types corresponded to mental traits. Sheldon and his associates have taken three aspects of bodily constitution, which they selected after many preliminary observations. These the authors call "endomorphy," "mesomorphy" and "ectomorphy." Illustrations show the types better than any words, but, briefly put, endomorphy can be described as the dominant component in the soft, round people with big viscera, mesomorphy means a predominance of muscle and bone and ectomorphy describes the lean, fragile, type with relatively large skin area and brain. The analogy with the three embryonic layers is obvious. In his psychiatric work Sheldon photographed about 3,000 young schizophrenic and about 300 manic-depressive patients. The hebephrenic and catatonic patients are highly ectomorphic as a group. The manic-depressive patients seem to be more mesomorphic than endomorphic. Paranoid types resemble these more than they resemble the catatonic or hebephrenic type. The book is interestingly written and well illustrated. Taken with the recent studies on the inheritance of schizophrenia and manic-depressive psychosis,[4] it makes the superficial classification of these as "functional psychoses" more indefensible than ever.

In "Mental Health,"[5] a volume of contributions by many speakers at the Christmas meeting 1938 of the American Association for the Advancement of Science, there is presented a great array of disconnected facts concerning mental disorders. The discussions at the end of each group of papers are carefully prepared and bring together the diverse data into coherent expositions. For instance, summarizing papers on genetics, syphilis, alcohol, vitamins and fatigue are correlated and discussed in an able chapter by Myerson. Other sections are on methods of research, environment, administration and education. The papers and their bibliographic references make the volume a most useful book for reference.

Brain has brought out a fourth edition of his series, "Recent Advances in Neurology."[6] It is written in clear style and is not marred by too

4. Kallman, F. J., and Rypins, S. J.: Genetics of Schizophrenia, New York, J. J. Augustin, 1938.

5. Moulton, F. R., and Komora, P. O.: Mental Health, Publication 9, American Association for the Advancement of Science, New York, Science Press, 1939, p. 470.

6. Brain, R. W.: Recent Advances in Neurology, ed. 4, Philadelphia, P Blakiston's Son & Co., 1940.

much abstracting and quotation; references are well chosen and plentiful. Of especial interest to internists are the chapters on headaches, sleep, the hypothalamus, micturition, viruses, deficiency disorders, disorders of muscle and meningitis.

HEADACHE

Brain's review of headache gives the background of experimentation in England by Pickering,[7] Northfield and others. In this country Wolff and his co-workers[8] have contributed important studies. They have shown that stretched cranial arteries give rise to certain headaches and that the large arteries at the base of the brain are responsible for the headache which follows intravenous injection of histamine. Extracerebral arteries make only a minor contribution to histamine headache,[9] but the headaches of migraine and hypertension are caused largely by dilatation of arteries in the scalp and dura. Penfield and McNaughton[10] believe that many headaches are caused by stretching the dura and dural sinuses. If diagnostic nerve block relieves the pain, radical neurectomy, or even operation on the dural lesion, will often cure the headache. The ophthalmic branch of the trigeminal nerve is the nerve most frequently involved. Wolff showed, furthermore, that the headache of migraine and that associated with hypertension were not relieved by increasing intracranial pressure, whereas histamine headache is reduced by increasing intracranial pressure. This is further evidence that the former kinds of headache are related to stretching of the arteries of the scalp. By observations on a particularly well trained patient they proved that the scotomas which come as prodromal warnings of a migraine attack are due to cerebral vasoconstriction. Thus the essentials of a migraine attack are cranial vasoconstriction followed by vasodilatation, but in the first case symptoms come from within the brain and in the second from the scalp and perhaps the dura. Treatment with amyl nitrite will relieve the first, while ligation of the appropriate branches of the common carotid artery will relieve the second.

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7. Pickering, G. W.: Brit. M. J. **1**:907, 1939.

8. Wolff, H. G.; Cahan, A. M., and Schumacher, G. A.: Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 6, 1940. Sutherland, A. M., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of the Mechanism of Headache in Migraine, Hypertension and Fever, Arch. Neurol. & Psychiat. **44**:929 (Nov.) 1940.

9. Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance in Headache, Arch. Surg. **41**:813 (Oct.) 1940.

10. Penfield, W., and McNaughton, F.: Dural Headache and Innervation of the Dura Mater, Arch. Neurol. & Psychiat. **44**:43 (July) 1940.

DEVELOPMENTS IN PSYCHIATRY

Since my review of the insulin treatment of schizophrenia in 1937,[11] the tide of enthusiasm rose to a flood amounting to thousands of shock treatments in various hospitals and now has ebbed, leaving much incidental knowledge that will eventually advance psychiatry. It is now demonstrated beyond reasonable doubt that repeated insulin shock destroys nerve cells in the brain.[12] It is probable that the mechanism is asphyxial, resulting from hypoglycemia. Meduna's convulsive therapy closely followed the insulin shock treatment, and is being even more widely used because the technic is simpler and less time consuming. Fits have even been given to patients in office practice! The treatment was originally designed to be used in cases of schizophrenia; this was because Meduna believed there was a "biologic anatagonism" between epilepsy and schizophrenia—a thesis which is based on no good evidence. Recently, however, it has been used for manic-depressive psychosis and neurosis and was even recommended by Meduna for epilepsy![13] Finley and Brenner[12] and others have shown that metrazol, like insulin, causes small islands of nerve cell destruction in the brain. The whole subject has been carefully and critically reviewed in three papers by Katzenelbogen.[14] He concludes by saying:

> The therapeutic achievements in schizophrenia have of late suffered a serious set-back, according to reports from many quarters. The loss in this field has been, however, amply compensated by the very favorable therapeutic results obtained in varied places in affective psychoses, and psychoneuroses. Emphasis is placed, as would be expected, mainly on shortening the duration of these disorders. While there appears to be justification for using convulsive therapy—which is not entirely devoid of danger to life and certainly of serious complications—in the last-mentioned conditions only if they are conspicuous by both severity and perseverance, it is to be regretted that this very drastic procedure is becoming routine practice. Instead of being reserved for special, particularly ominous conditions, it is being used rather indiscriminately, without due regard for the nature and seriousness of the illness, and without the circumspection such a procedure should command. For my part, I cannot help deploring the fact that the indiscriminate, universal use of "shock" and other supposedly short-cut therapies tends undeservedly to reduce the present-day treatment in psychiatry, to a level which turns the clock back to the Benjamin Rush epoch of the 18th century.

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11. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**:1098 (Dec.) 1937.

12. Finley, K. H., and Brenner, C.: Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 6, 1940.

13. von Meduna, L.: Read at the Ninety-Fifth Annual Meeting of the American Psychiatric Association, Chicago, May 8, 1939; Rev. neurol. e psychiat. de São Paulo **5**:101, 1939.

14. Katzenelbogen, S.: Psychiatry **2**:493, 1939; **3**:211 and 409. 1940.

I heartily endorse this opinion and merely add that to my mind only if the situation of the patient is hopeless enough to justify cerebral destruction for alleviation of symptoms does the treatment seem reasonable. To employ such drastic measures in treatment of recoverable mental disturbances, such as ordinary depression or neurosis, is unwarranted.

The new methods of shock therapy have had another result: They have awakened the medical enthusiasm of many psychiatrists who had been distrustfully watching the therapeutic pendulum swinging toward the side of the dynamic psychologists, who believe that all neuroses and at least some aspects of psychoses are explainable on the basis of disorganized interpersonal relations. Thus, insulin, metrazol, nitrogen asphyxia and electric shock were sometimes taken up, not with an enquiring scientific spirit, but with a desire to show the physicians of the psychologic school that mental ills were basically "organic."[15] The result is that the two camps in psychiatry, which were beginning to get together as physiologists and psychologists, are now tending to split apart again. This is a situation to be deplored; it leads to schism in the medical profession, intolerance and formation of new special societies. In contrast to the psychiatrists who treat neurosis with metrazol shock, take, for example, the position of Harry Stack Sullivan. In his William Alanson White lectures[16] Sullivan describes hysteria in a vivid manner:

> *Hysteria,* the mental disorder to which the self-absorbed are peculiarly liable, is the distortion of interpersonal relations which results from extensive amnesias. . . . In people who show our self-absorbed type of performances, however, the element of representative fantasy continues as a major ingredient of life. All sorts of interpersonal prehensions are fogged into what is called "wishful" distortions or misinformation about people. These people have no grey; everything tends to be black *or* white. Their friends are simply wonderful people. People whom they dislike are just simply impossible. Their "love" is melodramatic to a degree that confounds its object—excepting the object be another self-absorbed person. Together, by a sustained miracle of accommodating—or ignoring—the individualistic misconceptions of each other, two of these folk can have quite a good time. With the rest of us, however, they are apt to be disappointed, wounded, misunderstood. And we, if we care to study the processes at work, cannot but marvel at the failure of learning which has left their capacity for fantastic, self-centered, illusion so utterly unaffected by a life-long series of educative events. These people integrate situations with foggy embodiments projected upon us from their fantasies about themselves.

Such descriptions are too "true to life" (i. e., they agree with one's personal experience too well) to be ignored as not "scientific." One

15. For a discussion of the uselessness of the distinction between "organic" and "functional" conditions see my review of neuropsychiatry for last year (Arch. Int. Med. **64**:1333 [Dec.] 1939).

16. Sullivan, H. S.: Psychiatry **3**:1, 1940.

must accept the fact that observations made on the "higher functional activities of man," as Pavlov called psychologic reactions, can be controlled only in a limited way, just because of their complexity. The human organism is a very highly integrated unit; it acts as a unit as long as it is in normal health. It is only in disease, maladjustment or impossible environment that disintegration interferes with this normally smooth mechanism. Moreover, the breaking down of the unit into separate departments has no biologic basis, but is only the attempt of different academic departments to define their limits in the great field of biology. Psychologic phenomena are obviously the most complex of all functions of the body, but by this I am only stating that they are part of the physiology, although the most highly integrated part. In order to practice psychiatry one should insist on a training that gives to the physician both an understanding of human nature, as suggested in the quotation from Sullivan, and an understanding of the physiology of the brain and other organs. The need is for well balanced men trained in medicine, neurology and psychiatry.

The death of Austen Fox Riggs, on March 5, 1940, is a great loss to American psychiatry, for he was one of the pioneers in modern psychotherapy and throughout his life followed a sound middle course in his attitude toward mental ills and in his treatment of psychoneurotic patients. As far back as 1908 he stated emphatically:[17]

> The concept of psychophysiological unity is the basis of enlightened monistic philosophy and is the only concept which agrees with and is supported by the laws of nature.

He held to this belief that "psychology is only a sort of inclusive physiology"[18] throughout the thirty years of his neuropsychiatric practice. Many have since waged this war to uphold the unity of the human organism, but few have so steadily stuck to their guns and proved their points by successfully putting them into practice. He looked on suggestion as a biologic phenomenon that must be recognized and skilfully used by the physician, almost always indirectly, with avoidance of such crude technics as exhortation and hypnosis. He pointed out how frequently physicians undermined their good medical work through the adverse suggestion given to the patient by anxious or hurried manners and thoughtless words. Education was the mainstay of treatment; it was planned to give to the patient "knowledge of his difficulty, of his own assets and liabilities, and finally to teach him how to adjust himself to these difficulties.[19] As early as 1912 he taught that the person was made up of four levels anatomically and behavioristically—the reflex, the

17. Riggs, A. F.: M. Rec. **73**:1071, 1908.
18. Riggs, A. F.: Ment. Hyg. **6**:263, 1922.
19. Riggs, A. F.: Boston M. & S. J. **189**:269, 1923.

instinctive, the intelligent and the ethical.[20] He explained "nervousness" as arising on the basis of conflict between these levels, and he was fully aware of the effects of amnesia and how to get around this by letting the patient talk. His views were not widely known because he wrote little, but he taught many pupils and sent them out to practice and teach. Although he is gone, his work will go on through the Austen Riggs Foundation at Stockbridge, Mass., organized through the beneficence of his many devoted patients and carried on by the men he trained.

FUNCTION OF THE FRONTAL AREAS OF THE HUMAN BRAIN

The case of the "crow-bar skull" preserved in the Warren Museum at the Harvard Medical School, is the first instance reported[21] of an injury to the frontal areas of the brain that seemed to cause marked personality changes. The patient was an energetic and efficient foreman of road builders. On Sept. 18, 1848 he was tamping a blast into a drill in a rock when the powder exploded and drove the tamping iron through the left malar bone and orbit, into the left frontal pole of the brain and out through the vault of the skull a little to the right of the midline. He recovered miraculously but became "irreverent, profane and impatient of restraint" and was unable to hold a job. He died thirteen years later of epilepsy. Since then much experimental and clinical work has been done to elucidate the function of the frontal areas of the brain and to locate the seat of human "intelligence." Some of the animal work clearly forecast the results now found in the human subject. For example, Bianchi,[22] in 1893, after frontal ablations on monkeys, said that the animals no longer showed any restraint or resourcefulness in small difficulties and that "utilization of past experience was absolutely wanting." Shepherd,[23] in 1907, found that cats and monkeys lost recent memory, i. e., their training in opening a food box. Recently Fulton and his colleagues have done remarkable work on functional localization in the brains of the higher apes,[24] work which apparently led directly to operations on human patients, for Egas Moniz[25] mentioned the observation of Jacobsen[26] in Fulton's laboratory that a chimpanzee deprived

20. Riggs, A. F.: Talks to Patients, Stockbridge, Mass., 1912, p. 37; also in Coon, G. P., and Raymond, A. F.: A Review of the Psychoneuroses at Stockbridge 1940, Brattleboro, Vt., Hildreth & Co., 1940.

21. Harlow, J. M.: Publ. Massachusetts M. Soc. **2**:329, 1868.

22. Bianchi, L.: Mechanism of the Brain and the Function of the Frontal Lobes, Edinburgh, E. & S. Livingstone, 1922.

23. Shepherd, I.: The Frontal Lobes, 1907; cited by Bianchi.[22]

24. Fulton, J. F.: Physiology of the Nervous System, London, Oxford University Press, 1938.

25. Egas Moniz: Tentatives operatoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936.

26. Jacobsen, C. F.: A. Research Nerv. & Ment. Dis., Proc. (1932) **13**:225, 1934.

of her frontal areas, although less able to perform complex tasks, lost her anxiety over failure and seemed much more placid.

It was not only this experimental work which led to the present operation of "lobotomy" for agitated mental states, but the psychologic observation on certain cases in which operations for tumor had caused bilateral damage to the frontal areas of the cerebrum. Before describing these cases it is important to define just what is meant by the anatomic term "frontal area." The division of the brain into "lobes" is inexact and outmoded—frontal, parietal, occipital and temporal lobes are arbitrary morphologic divisions, with little biologic significance. It is now known that many areas of the cortex are recognizable by physiologic and histologic criteria that show the old division into "lobes" to be meaningless.

The "frontal" lobe is usually defined as all of that cortex and white matter lying in front of the central fissure of Rolando (figs. 1 and 2). This, then, includes the motor areas 4, 6 and 8, with the motor-speech area, 44, the frontal associative fields, 9, 10 and 11, and the triangular area, 45 with area 46 above it and area 47 below. On the mesial aspect of the hemisphere area 32, lying between the mesial parts of areas 11 and 8, should be included. These anterior zones (9, 10, 11, 32, 45, 46 and 47) constitute the "frontal areas," [24] and the terms "frontal lobectomy" and "frontal lobotomy" are usually used as meaning removal or undercutting of areas 9, 10, 11 and sometimes 32, 45, 46 and 47. The term "prefrontal lobe" seems to me illogical, in fact linguistically ridiculous, since an area cannot be in front of the front and since no anatomic fissure separates these areas off into anything like a lobe.

Starting with this definition, the question is: What is really known of the normal function of the frontal areas in man? Scientifically speaking, the answer must be: "Very little," because no case is known in which a normal man has been examined and then deprived of these areas and reexamined. Hebb and Penfield [27] say that it may be that no laboratory study will be adequate to reveal the defects that follow frontal injury because of the difficulty of obtaining good premorbid rating of ability. One must rely on observations concerning, first, brains already deformed and partially destroyed by tumors and, second, patients with epilepsy or mental symptoms who undergo cerebral operation for the relief of their symptoms. Obviously in neither case can satisfactory examinations be made before operation, so no scientific controls exist. The best one can do is to examine the cases and amass such data as are available. Harlow's case of the "crow-bar skull" has already been cited, but this is of more historical than neurologic interest, because the

27. Hebb, D. O., and Penfield, W.: Human Behavior After Extensive Bilateral Removal from the Frontal Lobes, Arch. Neurol. & Psychiat. **44**:421 (Aug.) 1940.

exact injury to the brain is not known; it had to be reconstructed from the skull specimen (fig. 1). The same can be said of a great deal of literature on the effects of frontal injuries in the last war. The data are interesting but not convincing. There is an extensive literature on unilateral lesions of the frontal areas. The more careful observers have been able to detect slight changes in personality (Penfield and Evans [28]), loss of initiative (Foerster [29]), loss of the power of abstraction (Goldstein [30]) and incapacity to resolve situations (Feuchtwanger [31]). Some authors, such as Grünthal,[32] have even expressed the belief that they can localize symptoms; for example, emotional distur-

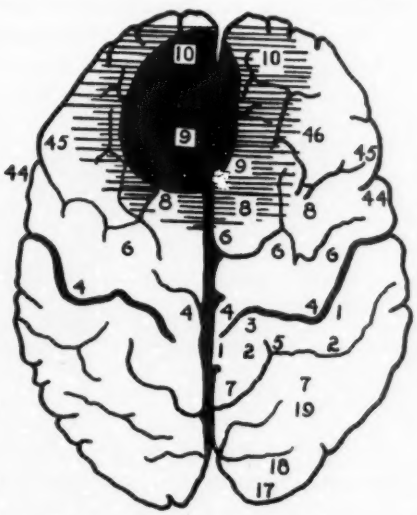

Fig. 1.—"The crow-bar" case from the Warren Museum at Harvard University (Harlow [21]). Reconstructed from the skull.

bances are likely to follow lesions of the orbital surface of the frontal lobe (area 11), whereas intellectual deterioration results from injury to the lateral convex surface (area 10). Nevertheless, after reading the reports of these numerous and extensive unilateral injuries, one is most impressed by the lack of symptoms.

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28. Penfield, W., and Evans, J.: Brain **58**:115, 1935.

29. Foerster, O.: Ztschr. f. d. ges. Neurol. u. Psychiat., 1918; cited by Rylander.[33]

30. Goldstein, K.: J. Neurol. & Psychopath. **17**:27, 1936.

31. Feuchtwanger, E.: Die Funktionen des Stirnhirns, Berlin, Julius Springer, 1923.

32. Grünthal, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:350, 1930.

Rylander,[33] of Stockholm, has given the results of the most recent and carefully controlled work in his monograph. It is superior to most of the previous work because careful psychologic tests were carried out in cases in which there were known operative lesions. He gives thorough reports of 32 cases in which part of one frontal lobe was removed for tumor or (in a few cases) for abscess; usually about two thirds of the lobe was removed, i. e., areas 8, 9, 10, 11 and 45, but in some instances the excision was smaller. Careful study of the case records, however, reveals that 16 of the patients probably had bilateral injury and 14 of these showed marked mental change. His follow-up examinations showed that in 25 cases there was "diminished inhibition of affective response" and in 20 distinct euphoria; in 14 cases restlessness was present and in 12 loss of initiative. Intellectual faculties were disturbed in 21 instances. These intellectual changes he specifies as: loss of attention, in 10 cases; slow thinking and lack of ability to "keep up," in 14; loss of memory for details, in 21; weak association, in 20, and poor memorization tests, in 11. Six patients showed a marked increase in appetite and weight with marked personality change. Rylander concludes:

> Mental changes occur after excision of parts of the frontal lobes. These changes are exhibited in alteration of personality. Generally they are not of such degree as to destroy the subject's ability to lead a normal social existence, but they can be fatal to persons doing qualified intellectual work.

Four cases have been reported in which both frontal areas were excised in order to remove a large tumor. The first and most carefully reported is Dandy's case; he operated on the man in 1930, and after prolonged and careful study Brickner published the psychologic observations in 1936. A reconstruction of the area removed from the left hemisphere is shown in figure 2 (black); from the right hemisphere a slightly larger excision was made, including probably a little more of area 8 and area 44. The results on the patient's mentality are given at length in Brickner's book[34]; briefly, the patient showed: (1) limitation of the capacity to associate and synthesize, e. g., distractibility with impairment of selection, retention and learning; (2) impairment of restraint of emotion with boasting, anger and hostility; (3) additional symptoms, such as impairment of abstraction, judgment and initiative, with euphoria and increased slowness, stereotypy and compulsiveness.

33. Rylander, G.: Personality Changes After Operations on the Frontal Lobes, London, Oxford University Press, 1939.

34. Brickner, R. M.: Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

Ackerly [35] reported a similar case in which an operation was performed in 1933 by Spurling. The left frontal area, however, though greatly compressed, was not actually removed. The symptoms were more like those reported by Rylander than by Brickner, but all have points of similarity. Euphoria was marked, and the patient said of the surgeon: "He cut out my worry!" The patient reported on by Karnosh [36] in 1935 showed emotional instability and distractibility. The patient in David and Askenasy's [37] case is interesting because she remarked after recovery, "I understand things better now, but they don't stir me up."

The most striking results, however, have come from the surgeons who have been performing "lobectomies" and "lobotomies" on psychotic patients for the relief of mental symptoms. As in the cases of tumor,

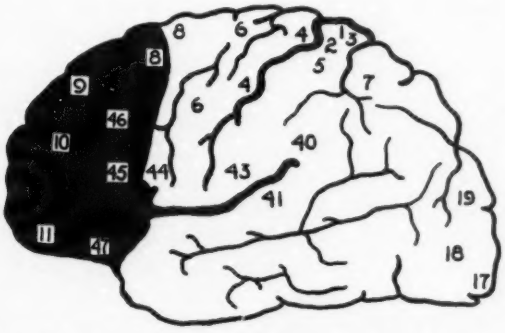

Fig. 2.—The left cerebral hemisphere in the Dandy and Brickner case, reconstructed from Brickner.[34] The amount of frontal lobe probably removed is shown in black.

one must admit that the evidence as to the normal function of the frontal areas is not convincing, because all the patients were psychotic before operation and there could be no normal controls. Moreover, as Hebb and Penfield [27] point out, disconnected and perhaps asphyxiated tissue is left in the brain after lobotomy, and this pathologic tissue may cause symptoms. Nevertheless, the mass of data accumulating is impressive and points in the direction already indicated by the cases of tumor previously cited. Egas Moniz started this form of treatment in Portugal, publishing his first results in 1936; since then he has done many more

35. Ackerly, S.: Am. J. Psychiat. **92**:717, 1935.
36. Karnosh, L. J.: J. Indiana M. A. **28**:567, 1935.
37. David, M., and Askenasy, H.: Encéphale **1**:34, 1939.

operations in various types of cases,[38] but the reports are so meager that one cannot judge of the work. In an earlier paper [39] he stated that the best results are with patients suffering from agitated depression. Of 20 cases, he produced cure in 7, amelioration in 7 and no effect in 6. Only 1 of the 20 cases, however, is given in enough detail to allow the reader to judge for himself as to the diagnosis and result.

In this country Freeman and Watts [40] and Lyerly [41] have taken up the work, and a few such operations have been done by other surgeons, notably Mixter,[42] who reported 2 cases of lobotomy with careful psychiatric examination and who in 1936 [43] performed a bilateral "frontal lobectomy" on a boy for epilepsy and noticed afterward that the patient lost his irritability and hostile attitude and became much easier to handle at home. Hebb and Penfield [27] have made the most recent and one of the best reports of a case of bilateral frontal lobectomy in a young man who was injured at the age of 16, was epileptic for ten years and was operated on at the age of 27. The studies are thorough from the points of view of psychology and anatomy. Their emphasis, however, is on the significance of the great improvement following the removal of abnormal frontal poles and the great diminution of abnormal electrical activity. The areas mutilated by the trauma were approximately 8, 9, 10 and 11, while the surgical procedure probably removed normal parts of areas 6, 8, 25, 32, 33, 46 and 47. The patient changed from an irresponsible, stubborn, restless and forgetful epileptic person to one with a "pleasant personality," who was "considerate of other patients" and had had only two seizures in fifteen months. The case demonstrates clearly the detrimental effect of the presence of pathologic lesions in the brain. The authors conclude from their psychologic examinations that removing a third of both frontal lobes need not cause gross deterioration. I believe, however, that the only cases that can be of much help in this problem are those of adult persons with personality traits well known before the trauma or disease.

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38. Egas Moniz: Am. J. Psychiat. **93**:1379, 1937; footnote 25.

39. Egas Moniz: Encéphale **31**:1, 1936.

40. Freeman, W., and Watts, J. W.: South. M. J. **30**:23, 1937; M. Ann. District of Columbia **6**:267, 1937; Yale J. Biol. & Med. **11**:527, 1939. Freeman, W.: Read before the International Neurological Congress, Copenhagen, August 1939.

41. Lyerly, J. G.: South. Surgeon **8**:426, 1939; J. Florida M. A. **25**:225, 1938.

42. Mixter, W. J.; Tillotson, K. J., and Wies, D. D.: Frontal Lobotomy in Two Patients with Agitated Depression: Therapeutic Evaluation and Further Reference to Function of the Frontal Lobes, Arch. Neurol. & Psychiat. **44**:236 (July) 1940.

43. Mixter, W. J.: Personal observation.

From the published papers it would seem that Freeman, Watts and Lyerly have done in all about 100 "prefrontal lobotomies." [44] The results of their work are summarized in the papers already referred to. This summarizing is the weakness of the work; only one adequate case report is given. Nevertheless, the results are interesting. The main symptoms relieved by the operation have been depression (80 per cent of 49 cases), agitation (70 per cent of 51 cases), compulsion (70 per cent of 27 cases), suspiciousness (55 per cent of 17 cases) and irritability (33 per cent of 14 cases). Symptoms produced have been inertia ("emotional flattening" or laziness), in most cases, hypomania (euphoria, playfulness and poor judgment), in about half the cases, and marked gain in weight in 40 per cent. Freeman and Watts divide their results into two classes: The primary results consist of inertia, lack of ambition, reduction in consecutive thinking, loss of "self consciousness," indifference to the opinion of others and satisfaction with results of inferior quality. The secondary results are euphoria, evasion, bluffing, talkativeness, aggressiveness, teasing, indecency in speech and act, inattention and poor judgment.

From the physiologic standpoint these operations of Egas Moniz, Freeman, Watts and Lyerly are of great interest. They indicate that in man bilateral loss of the frontal areas causes symptoms much like those postulated on the basis of animal experiments. Moreover, these operations indicate that the symptoms observed in cases of tumor and trauma of the frontal areas of the brain are specific for frontal lesions and occur only when the lesions are bilateral.

All observers agree that in cases of frontal lesions no especial quality of behavior is lost; it is rather as if there were a quantitative deficit. This, taken with all the other data, leads to the conclusion that the frontal areas (as well as some parietal and temporal regions) are associative areas. Stimuli reaching one or more of the receiving stations in the cortex (visual, auditory, tactile, etc.) spread rapidly through ever widening association paths to many areas of the cortex. This is a process of "long circuiting" [24] of the nerve impulses; there is delay in response; time and opportunity are given to the cerebral organ to respond to an outside stimulus in the light of past experience. I consider this the essential mechanism of intellect. It cannot be localized narrowly because its full effectiveness depends on its widespread topography and multiplicity of pathways. Lorente de Nó [45] has given a hint as to this

44. I cannot accept the term "prefrontal," as previously explained, nor do I think that "lobotomy" describes this partial severing of the white tracts from the frontal areas. It seems to me that "frontal leukotomy" would be a more descriptive name. Worst of all is Freeman and Watts's title "psychosurgery"—suggesting that one operates on the symptoms. Why not "vomitosurgery"?

45. Lorente de Nó, R.: J. Neurophysiol. **1**:187, 195 and 207, 1938.

complexity and its capacity for continued, "reverberating" function. Destruction of these "association areas," it seems to me, would give just such symptoms as the surgeons and their co-workers have described. What is needed is more observation of these patients before and after operation by trained psychiatrists and psychologists, who will present the data fully in each case, as Rylander, Hebb and Penfield, and Brickner have done. The summaries of most of the other authors, although suggestive and interesting, are not convincing as scientific evidence.

From the standpoint of therapy, "lobotomy" of the brain to relieve mental symptoms calls for careful consideration. Is the surgeon justified in depriving a patient of the most important part of his intellect in order to relieve him of emotional troubles? In the results as interpreted by the surgeons themselves, it is seen that such an operation usually leaves the patient lazy and undiscriminating. In other words, one often takes away the highest integration ("conscience," or "superego" perhaps) in order to make the patient happier. In my opinion this is a justifiable procedure only when the patient is old and the prognosis hopeless. Specifically, I can recommend the operation only in cases of prolonged agitated depression in persons over 60 years of age, or in rare instances in younger patients who show mental deterioration and neurologic and electroencephalographic evidence of cerebral degeneration. To perform such an operation on persons under 60 suffering from recoverable psychotic and neurotic states seems to me to be unjustified. Lastly, this "lobotomy" may well leave necrotic tissue and a scar that might later cause epilepsy. The procedure is so new that one has no evidence on this point, but such an outcome may be expected in a certain number of patients in from one to fifteen years.

News and Comment

Mississippi Valley Medical Society 1941 Essay Contest.—A cash prize of $100, a gold medal and a certificate of award are offered for the best unpublished essay on any subject of general medical interest, including medical economics, and of practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Cedar Rapids, Iowa, Oct. 1 to 3, 1941. Manuscripts should not exceed 5,000 words and should be typewritten in English. Five copies should be submitted, and they should be in the hands of the secretary, Dr. Harold Swanberg, W. C. U. Building, Quincy, Ill., not later than May 1, 1941.

The following officers for the ensuing year were elected at the meeting held November 17: Dr. E. P. Coleman, Canton, Ill., past chairman of the council of the Illinois State Medical Society, president; Dr. Dan G. Stine, Columbia, Mo., president-elect, and Dr. Harold Swanberg, Quincy, Ill., secretary-treasurer.

The Sixty-Ninth Annual Meeting of the American Public Health Association.—The meeting of the American Public Health Association and related organizations held in Detroit in October 1940 was the second largest in the history of the association.

The following officers were elected for the year 1940-1941: president, W. S. Leathers, M.D., Nashville, Tenn.; president-elect, John L. Rice, M.D., New York; treasurer, Louis I. Dublin, Ph.D., New York; chairman of executive board, Abel Wolman, Dr. Eng., Baltimore, and executive secretary, Reginald M. Atwater, M.D., New York.

The following Committee on Public Health in the National Defense was appointed: W. S. Leathers, M.D., chairman; Stanley H. Osborn, M.D.; Huntington Williams, M.D., and Abel Wolman, Dr. Eng.

A resolution was passed emphasizing the necessity for maintaining civilian health as essential in national defense and pledging the united support of members to the national defense and to the maintenance of health in a free people.

The next annual meeting will be held in Atlantic City, N. J., in October 1941.

Second Pan-American Congress of Endocrinology.—The second Pan-American Congress of Endocrinology will be held in Rio de Janeiro, Brazil, March 5 to 8, 1941. The congress will include symposiums on a great variety of lectures by outstanding authorities in the field, by invitation.

Membership in the congress is requisite to participation in the scientific sessions or receiving publications. Physicians who are interested may obtain further details from the secretary, Dr. Pedro A. Barcia, Casilla de Correo 255, Montevideo, Uruguay.

CORRECTION

In the article by Dr. Chester M. Jones entitled "Gastroenterology: Review of Literature from July 1939 to July 1940," in the October issue (ARCH. INT. MED. **66**:893, 1940), the name "Corey" in the first line on page 936 and in footnote 107 should be "Carey."

Book Reviews

Hipertension arterial nefrógena. By Juan Carlos Fasciolo. Pp. 155. Buenos Aires: Ferrari Hnos, 1939.

This is a comprehensive study of the nature of the hypertension that occurs in dogs after the suitable application of Goldblatt clamps to the renal arteries. In the first chapter technics for the measurement of the blood pressure of a dog are discussed and the author's preference for the method of Loman and Dameshek is defended. Chapter 2 reviews briefly experimental methods for producing hypertension in dogs. The distinctive features of the type of hypertension provoked by renal ischemia, as described by other workers, are noted, and Fasciolo presents his own experiments to confirm them. These features may be briefly noted:

1. Unilateral partial occlusion of a renal artery causes (usually) a temporary hypertension.

2. Partial occlusion of both renal arteries causes a persistent and more severe hypertension, which may not be accompanied, at least early, by the retention of nitrogenous material in the blood.

3. The hypertension resulting from unilateral clamping is: (*a*) augmented by removal of the normal kidney, or (*b*) cured by the removal of the ischemic one.

4. Partial occlusion of other visceral arteries does not provoke hypertension.

5. Unilateral or bilateral nephrectomy does not cause hypertension.

6. The elevation of blood pressure observed after the causing of renal ischemia is both systolic and diastolic.

With this background in mind Fasciolo examined the possible physiologic mechanisms for the production of this type of hypertension. Study of the literature satisfied him that the autonomic nervous system is neither responsible for the elevated blood pressure nor necessary for its production. He therefore performed experiments to determine the existence and nature of a humoral substance elaborated by the ischemic kidney and presumably destroyed by a normal one.

These experiments, in which he collaborated with Professor Houssay, are of the utmost interest. Earlier workers had attempted to find such a "humoral substance" by studying the action of various preparations of plasma or renal tissue extracts from hypertensive animals on certain test subjects. For reasons chiefly biologic the results of such studies have been equivocal from Tigerstedt's day to the present. The technic of Houssay and Fasciolo is biologically sound and relatively simple: The ischemic kidneys of dogs with hypertension were perfused by the carotid artery and jugular vein of a test dog. This animal was anesthetized with chloralose (chloral hydrate and dextrose), to preserve vasomotor reflexes, and was prepared for testing by having both kidneys removed. Chlorazol-fast pink was used as an anticoagulant, and the perfusion was carried out as expeditiously as possible. Many such perfusion experiments were performed. When the ischemic kidneys of dogs with hypertension were perfused, the blood pressure of the host rose promptly from 25 to 70 mm. of mercury. Perfusion of normal kidneys rarely caused any alteration of the pressure of the host. One interesting experiment was performed on a kidney that had two renal arteries arising independently from the aorta, on one of which a Goldblatt clamp had been placed. The other kidney of this dog had been removed, and hypertension was present. The renal artery that had not been clamped was perfused first, and no variation of the blood pressure occurred. After twenty-five minutes the perfusion cannula was switched to the clamped artery and the ischemic zone of the kidney perfused.

Within six minutes the blood pressure of the host rose from 150 to 190 mm. of mercury. In several experiments there was performed on one host successive perfusion by both kidneys of a dog in which hypertension had developed after the clamping of only one renal artery. In such experiments the normal kidney had no effect on the blood pressure, whereas the ischemic one caused a prompt elevation of the pressure of the host. This same type of experiment demonstrated conclusively that normal renal tissue was able to nullify the effect of the hypertensive substance. Similar experiments demonstrated that the adrenal glands, the pituitary and the thyroid gland and the gonads were neither necessary for the production of the hypertension nor able to prevent its development.

One chapter of the monograph reports Fasciolo's experience with the Lüwen-Trendelenburg technic of perfusing the vascular system of a toad with citrated plasma of hypertensive dogs. Fasciolo reports that blood from the renal vein of an ischemic kidney caused an average diminution of 63 per cent in the flow of blood through this preparation. Blood from normal kidneys caused an average decline of 2.8 per cent. The remainder of the monograph dealing with histologic changes in the kidneys and retinas of hypertensive dogs is of less significance than the part just reviewed.

The monograph closes with a brief and sober chapter on the surgical treatment of hypertension. On the basis of the experiments discussed, one would anticipate no benefit from neurosurgical or endocrinologic operations for hypertension due to renal ischemia. In patients with such hypertension if renal disease is unilateral, nephrectomy is advisable; while for patients in whom it is bilateral, revascularization operations are suggested. The author admits that if hypertension is neurogenic he is unable to evaluate fairly the procedures suggested on the basis of his experiments.

Clinical Roentgenology of the Alimentary Tract. By Jacob Buckstein, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York; Consultant in Gastroenterology, Central Islip Hospital. Price, $10.00, cloth. Pp. 652, with 525 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This volume, by a roentgenologist with experience in roentgenology of the alimentary tract of twenty years at Bellevue Hospital in New York, is the latest contribution to gastroenterology and roentgenology. In general, the work is fairly complete and includes sufficient detailed description of functional and organic changes of the alimentary tract to serve as an approach to the best means of roentgenographic diagnosis in actual clinical practice. An effort has been made throughout to correlate etiologic and pathologic observations with the characteristic roentgen observations.

Attention has been devoted to the variations in the roentgen appearances of the normal organs of the gastrointestinal tract. Of value is the author's consideration of differential diagnosis relative to each clinical condition. Throughout the book points of importance are stressed by the use of italics. Brief reports and reproductions of roentgenograms of illustrative cases are included.

The book, consisting of fifty-eight chapters, is divided into eight main sections which cover the following subjects: esophagus; stomach; duodenum; small intestine; large intestine; herniation and eventration of the diaphragm; gallbladder and bile ducts, and, finally, spleen, liver and pancreas. The discussions of the value of the roentgen examination and the correlation of the pathologic changes with the roentgen appearance of the healing process in gastric and duodenal ulcers are timely. Of interest also is the author's consideration of chronic gastritis and duodenitis.

This book should serve as a valuable reference for any physician interested in the study of the alimentary tract. The text is clear and practical, and the illustrations are excellent. A fairly complete and indexed bibliography and a general index are included.

Brucellosis in Man and Animals. By I. Forest Huddleson, D.V.M., M.S., Ph.D., Research Professor in Bacteriology, Michigan State College; A. V. Hardy, M.S., M.D., Dr.P.H., Associate Professor of Epidemiology, Columbia University Medical School; J. E. Debono, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics Royal University of Malta; Ward Giltner, D.V.M., M.S., Dr.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Price, $3.50. Pp. 339, with 41 illustrations. New York: The Commonwealth Fund, 1939.

The Commonwealth Fund has financed the publication of many excellent monographs. Included among this splendid group is the book by Huddleson and his contributing authors on "Brucellosis in Man and Animals," a revision of the manual "Brucella Infections in Animals and Man," which came out in 1934. The revision is much larger and much more inclusive than the original volume. The initial forty-five pages of the book have to do with the bacteriology of the genus Brucella. This section is valuable to the laboratory worker and to the clinician, for it contains many excellent suggestions and much information concerning this interesting group of bacteria. To the clinician the next hundred pages are of primary importance, for they give a thorough and complete presentation of the important features of the disease brucellosis. After this is a section devoted to brucellosis in Malta, and then follows a section on treatment. The last part of the book gives a considerable amount of laboratory data on man and cattle.

Brucellosis in animals concerns the student of public health and the veterinarian. From a recital of the divisions of the book it is obvious it was not written for the clinician alone, but also for others who have to do with the disease.

The very complete bibliography, the excellent illustrations and the superb format of the book make it an outstanding example of the publishers' art. Adverse criticisms of its contents would be few and far between. One such criticism would be that it is doubtful that Brucella melitensis vaccine is as effective in the treatment of brucellosis as the authors have suggested. On the whole, most clinicians have had unfavorable results and have judged the preparation to be of little value; however, their technic of administration of such vaccine may have been faulty.

Verhandlung der Deutschen Gesellschaft für Kreislaufforschung. Pp. 424. Dresden and Leipzig: Theodor Steinkopff, 1939.

This is a report of the transactions of the twelfth annual meeting of the German Society for Study of the Circulation, which has 517 members. Since there were thirty-three presentations at the aforementioned meeting, all of which are printed in this volume, it is obviously impossible to give more than a scanty review of the contents. The chief subjects presented in this collection of individual articles are electrocardiography and cardiac failure. There are twenty-one presentations on electrocardiography, including such diverse subjects as "A new cathode ray electrocardiograph," "Electrocardiography in gun shot wounds of the heart," "The conduction system in auricle and ventricle, particularly in horses" and "On the question of injury of heart muscle in diabetic coma."

There is a symposium on "therapy of heart failure" which includes presentations of the physiologic and of the pharmacologic aspects of heart failure, as well as an extensive article by Volhard on treatment. Two guest lectures are printed, one on the "physiologic effects of extensive sympathectomy for essential hypertension" and one on "the circulation of the kidneys in experimental glomerulonephritis and the effects of denervation of them." There are additional presentations on such subjects as physiologic and pathologic changes in heart volume, and heart failure in diphtheria.

This is essentially a book for the cardiologist, who should find much of interest in it. One implication is that in Germany the study of the circulation is still essentially the study of the heart, for in this volume there is almost no consideration of the peripheral circulation.

Diseases of the Gallbladder and Bile Ducts. By Waltman Walters and Albert M. Snell. Price, $10. Pp. 645, with 342 illustrations in 195 plates. Philadelphia: W. B. Saunders Company, 1940.

This well printed and finely illustrated book, written by thorough experts, contains about all there is for the physician to know about diseases of the biliary tract. Beginning with the history of the subject and ending with the latest word on treatment, what is said, one feels throughout, is based on wide personal experience and is not mere "prattle without practice." The chapters on special topics by some of the other staff members of the Mayo Clinic, such as those on physiology by Bollman and on radiology by Kirklin, are also satisfactory.

Indeed the reviewer's only criticism is that in the effort to omit nothing the authors have indulged in a good deal of needless and confusing repetition. Chapter 4 (part II), for example, concerns "Chronic Cholecystic Disease," but later, in chapter 8, "Calculous and Non-Calculous Cholecystitis" is dealt with and the same material is to some extent gone over again. But neither of these chapters considers treatment, which is deferred to chapter 1 of part IV, again with some repetition. In brief, the reviewer believes that the book could have been done in much shorter space with corresponding reduction in price. Time was when diseases of the liver and bile ducts were dealt with in one moderately priced volume; now one has to pay a large sum for a book on the bile ducts alone. This general tendency toward expensive books on limited clinical subjects is to be deplored. If the physician has to buy separate treatises on numerous conditions, such as pneumonia, arterial occlusion of the legs and angina pectoris, the problem of the library becomes difficult, and with few exceptions these narrow clinical monographs contain much inert padding.

Die Ergebnisse der Sternalpunktion. By Norbert Henning and Heinz Keilhack. Price, 12 marks. Pp. 90, with 19 illustrations (some in color). Berlin: Julius Springer, 1939.

The merits of sternal puncture technic for the study of human bone marrow have received considerable attention in the past few years. Monographic studies of Nordenson (1935) and Segerdahl (1935) have been previously reviewed in the ARCHIVES OF INTERNAL MEDICINE. This monograph brings the literature on this subject up to date, and a commendable bibliography is appended. Sternal puncture is undoubtedly here to stay as a diagnostic procedure. Now that the wave of enthusiasm over a new technic has subsided and the limitations of this method have been closely demarcated by those still advocating a complete biopsy technic, clinicians have settled back to find that bone marrow studies are of only relatively rare diagnostic importance. Bone marrow puncture studies in cases of pernicious anemia, hemolytic icterus, polycythemia, agranulocytosis, purpura and ordinary leukemia, while informative and constructive in helping formulate ideas concerning the underlying pathologic function of these conditions, are not necessary to a clinical diagnosis. The true diagnostic value of sternal puncture (marrow) lies in the realms of aleukemic leukemia, multiple myelomas, Gaucher's disease and the so-called refractory anemias. Even in cases of these disorders negative findings are in no way conclusive. For those interested in hematology, this monograph is to be recommended.

Abortive Poliomyelitis. By Dr. Otto Gsell. Price, 6.70 marks. Pp. 93, with 13 illustrations and 19 tables. Leipzig: Georg Thieme, 1938.

The author considers a number of phases of poliomyelitis. After a brief introduction and historical background, the epidemiology is discussed at some length, not only in regard to local epidemics but also in regard to those of other parts of the world, e. g., Denmark and California. The benign course of the disease in the California epidemic is pointed out as in contrast to the high degree of infectivity. The greater the incidence of poliomyelitis from year to year, the more prevalent the abortive form is apt to be.

Pharyngitis and signs of infection of the respiratory tract are associated with the purely abortive form, which clinically often has no nervous system manifestations. The meningitis of Bang's disease, of Weil's disease, of syphilis and of infectious exanthema, are considered with respect to differential diagnosis. The prognosis of the purely abortive form is good; the temperature falls in three to five days, and clinical recovery is apparent in one to two weeks, with no residual signs. A short chapter is devoted to the prophylaxis and treatment of poliomyelitis.

This monograph should be of particular interest to those who are active in this field.

The Vasomotor System in Anoxia and Asphyxia. A Study of the Adjustment Reactions of the Mammalian Organism. By Ernst Gellhorn, M.D., Ph.D., and Edward H. Lambert, M.D. Joint Contribution from the Department of Physiology of the College of Medicine of the University of Illinois and from the Psychiatric Institution of the State Department of Public Welfare. Paper, $1.00. Pp. 69, with 21 figures. Urbana, Ill.: University of Illinois Press, 1939.

This is a monograph which records the results of experimental observations concerning the effect of both anoxia and asphyxia on the vasomotor mechanism. The authors sharply distinguish between these two conditions, and according to the results of their studies such distinction must be made between the mere absence of oxygen and the absence of oxygen combined with the presence of carbon dioxide. The methods of study are carefully given and the results evaluated. The modes of action of the vasomotor system are considered and explained. Carotid sinus reflexes and the respiratory and circulatory adjustment to the experimental conditions are discussed in detail. The bibliography is extensive and complete.

Blood Groups and Blood Transfusion. By Alexander S. Wiener. Price, $5. Second edition. Pp. 306, with 25 figures and 84 tables. Springfield, Ill., and Baltimore: Charles C. Thomas, 1939.

This handsome monograph, finely printed and well illustrated, covers the subject of blood groups and blood transfusion in a thoroughly satisfying way. There are definitive discussions of the history of the subject, of the practical aspects of blood typing and of the technic of transfusion. The scholarly chapters on the heredity of the blood group may be fairly heavy going for clinical readers but are invaluable for reference. The book is well documented throughout with references to the literature.

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